

THE AMERICAN JOURNAL OF PSYCHIATRY

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The Movement Toward Integrating the Psychotherapies:
An Overview

By Bernard D. Beitman, Marvin R. Goldfried, and John C. Norcross

A Neuroanatomical Hypothesis for Panic Disorder

By Jack M. Gorman, Michael R. Liebowitz, Abby J. Fyer, et al.

How Are Depression and Bulimia Related?

By Alan B. Levy, Katharine N. Dixon, and Stephen L. Stern

Special Section:

Dangerousness and the Civil Commitment Process

Official Journal of the American Psychiatric Association

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References: 1. Newton RE, et al. A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Moskowitz H and Smiley A. Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12, Sec 2):45-55. 3. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: General—Interference with cognitive and motor performance: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the

syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation in-

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cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: tachycardia/palpitations 1%. *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal*: Musculoskeletal aches/pains 1%. *Neurological*: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin*: Skin rash 1%. *Miscellaneous*: Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of

breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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A man with dark, wavy hair and a slight smile is leaning on a light-colored wooden railing. He is wearing a red, white, and black plaid button-down shirt over a black t-shirt, and a black belt with a silver buckle. The background shows a building with light-colored siding and a dark doorway. The lighting is warm, suggesting an indoor or evening setting.

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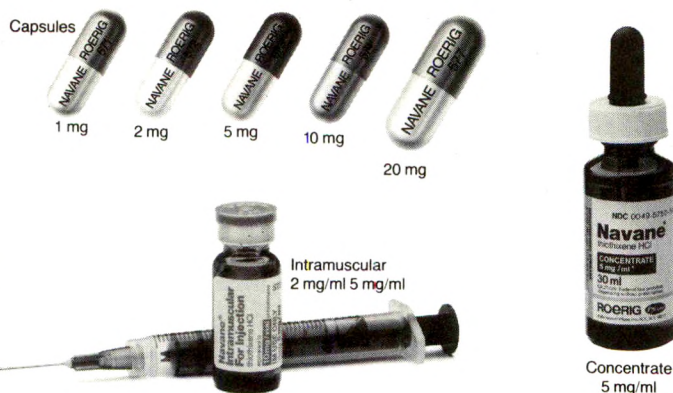
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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: **Tardive Dyskinesia**—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients use the lowest possible dose. (See Dosage and Administration). Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tired-

ness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea, vomiting, and increased salivation. **Cardiovascular:** Tachycardia/palpitations, and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings).

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecostasia and galactorrhea have been reported but no causal relationship

was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED

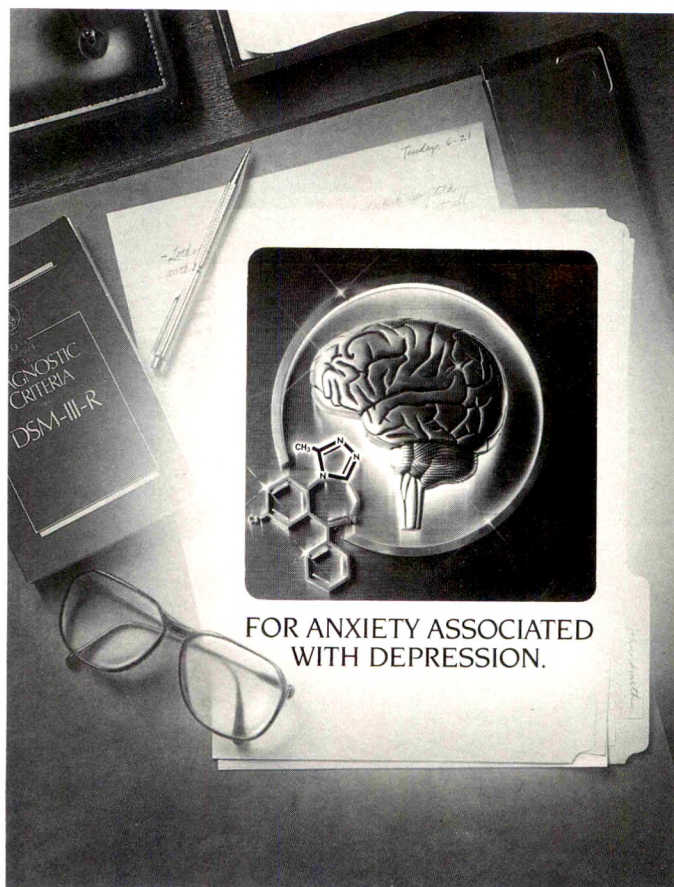
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ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information, on adjacent page, especially **Warnings** and **Information for the Patient** sections.



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ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 6 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

- ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder.
- ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., phenoloths, methylphenidate and amphetamines) and such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
- Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
- ORAP is contraindicated in patients with severe local central nervous system depression or comatose states from any cause.
- ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following (see also PRECAUTIONS—Information for Patients).

Tardive Dyskinesia. A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients receiving antipsychotic drugs. Although the prevalence of the syndrome appears to be higher among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the location of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS—Information for Patients.)

Neuroleptic Malignant Syndrome (NMS). A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinuria) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central adrenergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any complicating serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reoccurrence of drug toxicity should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hypotension, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other. Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg, or less. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a neuroleptic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decision to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General. ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys. Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests. An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium deficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions. Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such

as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about three times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in mice.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased progenies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryofetal loss including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery. This drug has no recognized use in labor or delivery.

Nursing Mothers. It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited. Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General. Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported infrequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, oculobulbar crises) have been reported for less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinsonian drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Extrapyramidal Reactions. Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience tardive dyskinesia signs after abrupt withdrawal. In certain of these cases the tardive dyskinesia movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal extrapyramidal signs or if such further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary involvements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vibratory movements of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hypertension: Hypertension has been reported with other antipsychotic drugs.

Clinical Trials: The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	0	1
Nausea	1	2
Vomiting	0	1
Constipation	4	2
Eruptions	0	1
Thirst	1	0
Appetite Increase	1	0

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Slumped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Inattention	2	2
Dizziness	0	1
Ataxia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Altered	6	0
Psychiatric		
Depression	2	3
Excitement	1	0
Nervous	1	0
Adverse behavior	6	0
Special Senses		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes	1	0
Increased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigation experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions. In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema.
Cardiovascular/Respiratory: Postural hypotension, hypotension, hyperbaric, tachycardia, palpitations.
Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress.
Endocrine: Loss of libido.
Metabolic/Nutritional: Weight gain, weight loss.
Central Nervous System: Dizziness, tremor, parkinsonism, ataxia, dyskinesia.
Psychiatric: Excitement.
Skin: Rash, sweating, skin irritation.
Special Senses: Blurred vision, cataracts.
Urogenital: Nocturia, urinary frequency.

Postmarketing Reports. The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia.

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be in comparison of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinsonian medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdoses.

DOSEAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief obtained is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS—Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent that identified. In attempts to reduce the dosage of ORAP, caution should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal-related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

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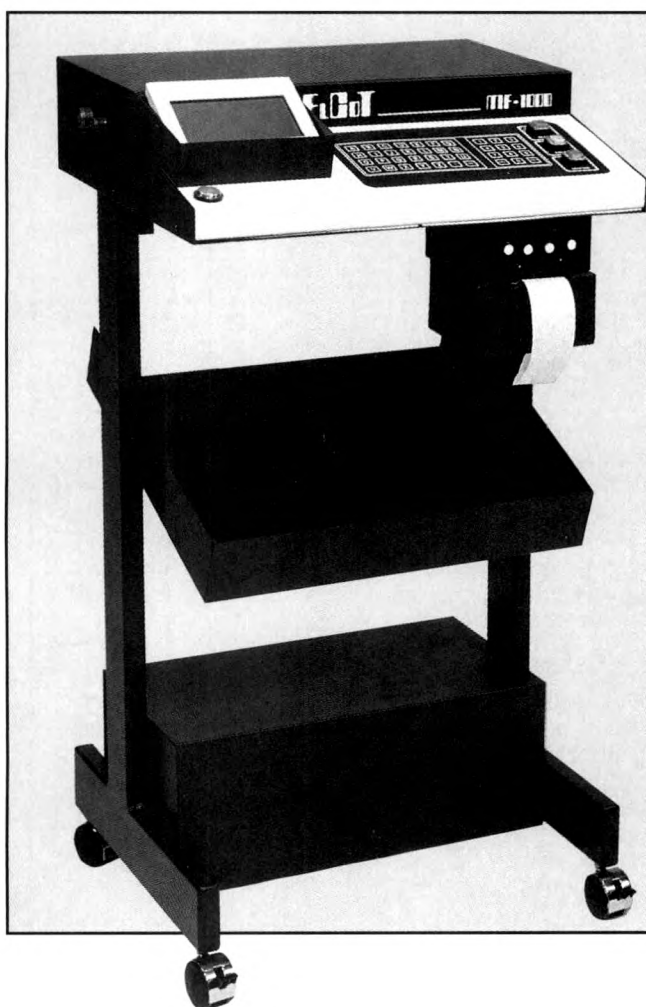
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1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

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APRIL

April 2-5, Geriatric Medicine 1989 Symposium, Division on Aging, Harvard Medical School, Boston. Contact the Department of Continuing Education, Harvard Medical School, Boston MA 02115; 617-732-1525.

April 4-9, annual meeting, American Association of Pastoral Counselors, St. Louis. Contact Barbara L. Gyomory, Director of Administration, 9508 A Lee Highway, Fairfax, VA 22031; 703-385-6967.

April 6-8, 7th Annual Bulimia Anorexia Self-Help/Behavior Adaptation Support and Healing (BASH) International Conference on Eating and Mood Disorders, St. Louis. Contact Félix E.F. Larocca, M.D., 6125 Clayton Avenue, Suite 215, St. Louis, MO 63139; 800-227-4785 or 314-567-4080.

April 6-8, semiannual meeting, Group for the Advancement of Psychiatry, White Plains, New York. Contact Jerry M. Lewis, M.D., President, P.O. Box 330, Greenbelt, MD 20770; 301-345-8030.

April 12-16, annual meeting, American Association of Suicidology, San Diego. Contact Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

April 13-16, annual meeting, American College of Physicians, San Francisco. Contact John Ball, M.D., J.D., F.A.C.P., Executive Vice-President, 4200 Pine Street, Philadelphia, PA 19104; 215-243-1200.

April 13-19, annual meeting, American Academy of Neurology, Chicago. Contact Jan W. Kolehmainen, Executive Director, AAN, 2221 University Avenue, SE, Suite 335, Minneapolis, MN 55414; 612-623-8115.

April 16-19, annual meeting, American Occupational Therapy Association, Baltimore. Contact Executive Director, 1383 Piccard Drive, Rockville, MD 20850; 301-948-9626.

April 27-30, American Association for the History of Medicine, Inc., Birmingham, Alabama. Contact Edward C. Atwater, M.D., Secretary-Treasurer, 601 Elmwood Avenue, Rochester, NY 14642; 716-275-2903.

April 27-30, annual meeting, National Council on Alcoholism, Inc., Atlanta. Contact Thomas V. Seesel, Executive Director, 12 West 21st Street, 7th Floor, New York, NY 10010; 212-206-6770.

April 30-May 5, annual meeting, American Occupational Medical Association, Boston. Contact Donald L. Hoops, Ph.D., Executive Director, 55 West Seegers Road, Arlington Heights, IL 60005; 312-228-6850.

MAY

May 1-5, annual meeting, American Pediatric Society, Washington. Contact Audrey Brown, M.D., Secretary-Treasurer, 450 Clarkson Avenue, Brooklyn, NY 11203; 718-270-1692.

May 3-7, annual meeting, American Psychoanalytic Association, San Francisco. Contact Helen Fischer, Administrative Director, 309 East 49th Street, New York, NY 10017; 212-752-0450.

May 3-7, annual meeting, Society of Biological Psychiatry, San Francisco. Contact David L. Dunner, M.D., Secretary-Treasurer, Harborview Medical Center ZA-15, Seattle, WA 98104; 206-223-3425.

May 4-7, annual meeting, American Association of Sex Educators, Counselors and Therapists, Washington. Contact Ruth Hunt, Ph.D., Executive Director, 11 Dupont Circle, NW, Suite 220, Washington, DC 20036; 202-462-1171.

May 4-7, annual meeting, American Academy of Psychoanalysis, San Francisco. Contact Vivian Mendelsohn, Executive Director, AAP, 30 East 40th Street, Room 206, New York, NY 10016; 212-679-4105.

May 5-7, annual meeting, American Society for Adolescent Psychiatry, San Francisco. Contact Mary D. Staples, Executive Secretary, 24 Green Valley Road, Wallingford, PA 19086; 215-566-1054.

May 6, annual meeting, American College of Psychoanalysts, San Francisco. Contact Harold Mann, M.D., Secretary Gen-



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References: 1. Thompson TL II, Thompson WL. Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(August):87-109. 2. Georgotas A. Affective disorders: Pharmacotherapy. In Kaplan HL, Sadock BJ (eds). *Comprehensive Textbook of Psychiatry IV*. Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. 3. Roose SP, Glassman AH, Siris SG, et al. Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Psychopharmacol* 1981;1:316-319. 4. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In Gilman AG, Goodman LS, Rall TW, et al (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. 5. Thygesen P, Bjerre M, Kragh-Sorensen P, et al. Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. 6. Blackwell B, Peterson GR, Kuzma RJ, et al. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol* 1980;4:255-261. 7. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. 8. Bye C, Clibbey M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. 9. Kupfer DJ, Spiker DG, Rossi A, et al. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry* 1982;17:535-546.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor[®] (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor[®] (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop.

Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car, therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy: Safe use during pregnancy and lactation has not been established, therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children: Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

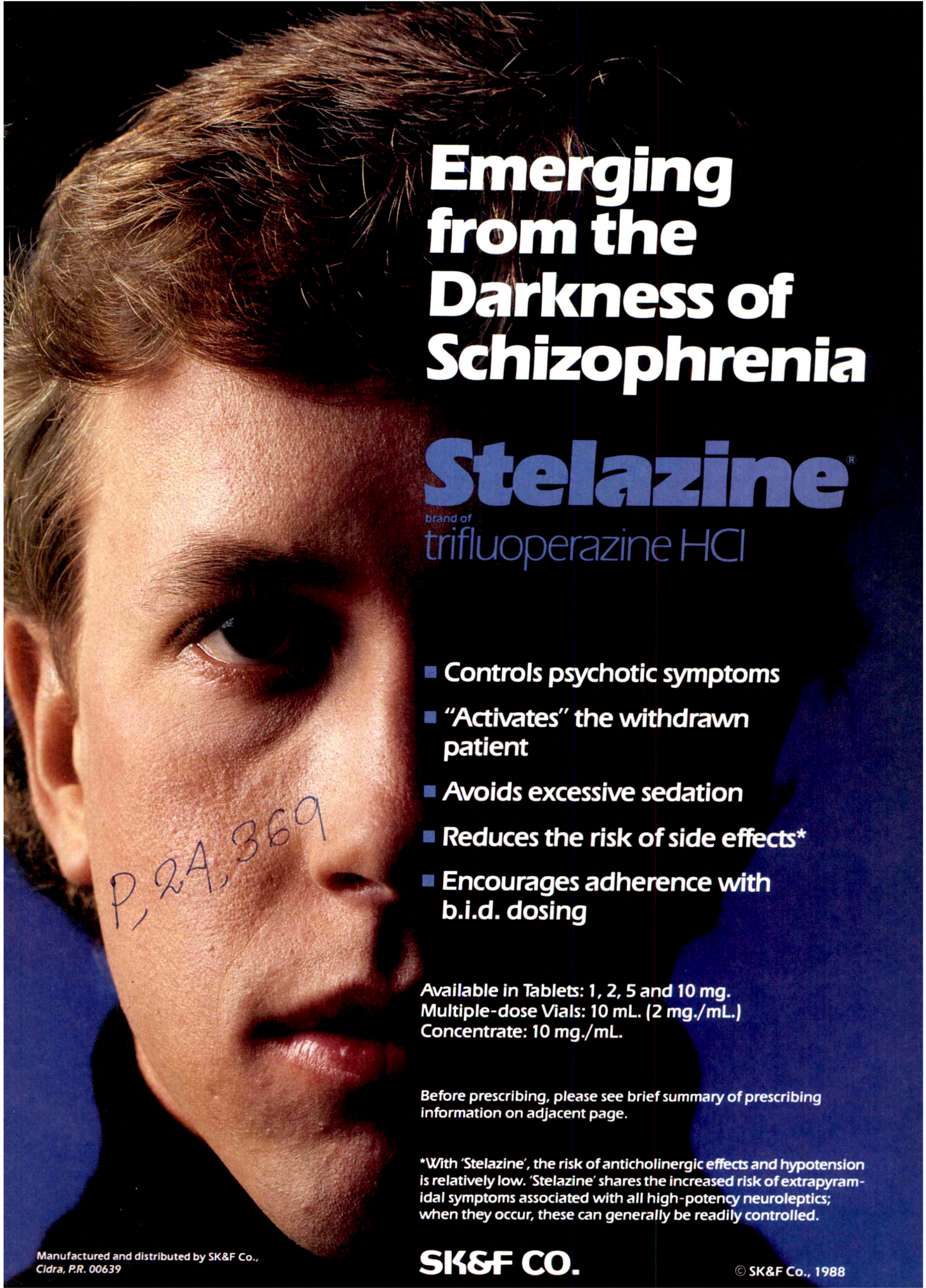
Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hyperten-

sion, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block; stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, panic, nightmares, hypomania, exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone-marrow depression, including agranulocytosis, eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue, headache, parotid swelling, alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

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Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperreflexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuation of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders [e.g., mitral insufficiency or pheochromocytoma].

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecostasia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines [apparently due to cardiac arrest or asphyxia due to failure of cough reflex] has been reported.

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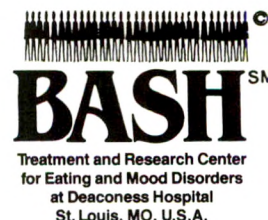
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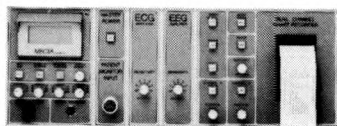


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Introductory Remarks

Marc Schuckit, MD, Professor

University of California San Diego:

Substance Abuse and Dual Diagnosis

James Shore, MD, Professor and Chairman

University of Colorado:

Substance Abuse and the Disabled

Robert Cabaj, MD, Clinical Associate in Psychiatry

Harvard Medical School:

Substance Abuse and the Gay Community

Sheila Blume, MD, Medical Director

Alcoholism, Chemical Dependency and

Compulsive Gambling:

Substance Abuse and Women

Dale Walker, MD, Professor

University of Washington:

Substance Abuse and Ethnic Minorities

Small Group Discussions:

Informal group discussion with presenters and distinguished members of organization

SUNDAY, May 7 Morning

Timmen Cermak, MD, Assistant Professor

University of California:

Adult Children of Alcoholics

Joseph Westermeyer, MD, Professor

University of Minnesota:

Discussion on ACOA Movement

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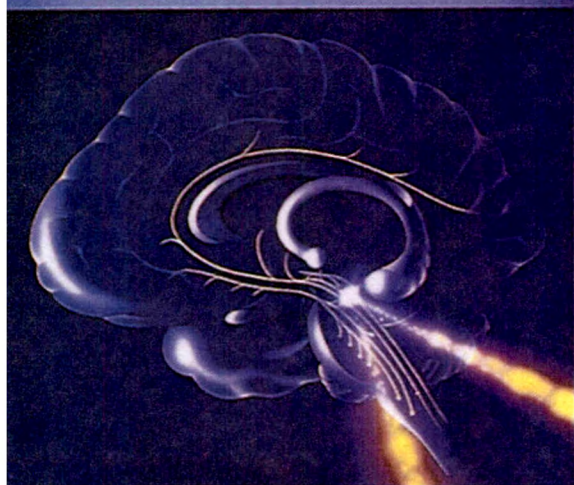
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Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

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Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

Avoid using MAO inhibitors concomitantly or in proximity to Prozac

Rash and/or urticaria occurred in 4% of clinical trial patients

A wide margin of safety

20-mg once-a-day therapy

PROZAC...
*A specifically different
antidepressant*



1. *Curr Ther Res* 1986;39:559-563.
*As defined by DSM-III.

*See adjacent page
for brief summary of
prescribing information.*

Prozac® fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monamine Oxidase Inhibitors*—Data on the effects of the combined use of fluoxetine and MAOI inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,000 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever; leukocytosis; arthralgias; edema; carpal tunnel syndrome; respiratory distress; lymphadenopathy; proteinuria; and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknown at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: **General—Anxiety and Insomnia**—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo and 3% of tricyclic antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Manic/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of manic/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, only adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine. It should be used with caution in such patients.

Interference With Coagulation and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (i.e., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—See Warnings.

Other Antidepressants—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and Slow Elimination under Clinical Pharmacology).

Diazepam—Clonazepam—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (see Accumulation and Slow Elimination under Clinical Pharmacology).

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Use in Children—Safety and effectiveness in children have not been established.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hypotension—Several cases of hypotension (some with serum sodium lower than 110 mmol/L) have been reported. The hypotension appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: Commonly Observed—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (6.3%), primarily nervousness, anxiety, and insomnia; digestive (5.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=796)		Prozac (N=1,730)	Placebo (N=796)
Nervous			Body as a Whole		
Headache	20.3	15.5	Anxiety	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	11.8	7.1	Pharyngitis	1.6	1.1
Drowsiness	11.8	8.3	Fever	1.4	—
Anxiety	9.4	8.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	6.7	3.3	Arthritis	1.2	1.5
Fatigue	4.2	1.1			
Sweating	1.9	1.3	Respiratory		
Sensation			Upper		
Disturbance	1.7	2.0	Respiratory	7.8	6.0
Likelihood	1.6	—	Pain, joint	2.8	1.9
Decreased	1.6	—	Pharyngitis	2.7	1.3
Light			Nasal	2.6	2.3
Headaches	1.6	—	Cough	2.3	1.8
Concentration,	1.5	—	Sinusitis	2.1	2.0
decreased	1.5	—	Cough	1.9	1.6
			Conjunctivitis	1.4	—
Digestive			Cardiovascular		
Nausea	21.1	10.1	Heart	1.8	1.0
Diarrhea	12.3	7.0	Palpitations	1.3	1.4
Stomach	9.5	6.0			
Cramps	6.7	1.5	Musculoskeletal		
Dyspepsia	6.4	3.3	Pain, back	2.0	2.4
Constipation	4.5	3.3	Pain, joint	1.2	1.1
Pain,	3.4	2.9	Pain, muscle	1.2	1.0
abdominal	2.4	1.3			
Vomiting	2.4	1.3	Unlabeled		
Flatulence	1.6	1.1	Manufacture,		
Gastroenteritis	1.0	1.4	pellet	1.9	1.4
			Social		
Skin and			isolation	1.9	—
Appendixes			Frequent		
General	8.4	3.8	relaxation	1.6	—
Swallowing	2.7	1.8	Urinary tract		
Rash	2.4	1.4	Infection	1.2	—
Pruritus	2.4	1.4			
			Special Senses		
			Vision		
			disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
— Incidence less than 1%.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unlabeled events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (to, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, whose COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—Frequent: chills; infrequent: chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdominal enlargement, cellulitis, hydrocephalus, hypothermia, LE syndrome, monilia, and serum sickness.

Cardiovascular System—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block (first-degree), bradycardia, bundle-branch block, central ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—Frequent: increased appetite; infrequent: anorexia, stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, pancytopenia, purpura, sedimentation rate increased, and thrombocytopenia.

Metabolic and Nutritional—Frequent: weight loss; infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesterolemia, hyperglycemia, hypokalemia, hypoglycemic reaction, hypocalcemia, hypomagnesemia, and iron deficiency anemia.

Musculoskeletal System—Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrocytopenia, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—Frequent: abnormal dreams and agitation; infrequent: abnormal gait, acute brain syndrome, ataxia, amnesia, apathy, ataxia, buccopharyngeal syndrome, CNS stimulation, convulsions, dizziness, depression, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hyperthermia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electroencephalogram, anticholinergic reaction, chronic brain syndrome, circumscribed paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertension, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—Frequent: bronchitis, rhinitis, and yawn; infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/atelectasis, and pleural effusion.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpura, rash, pustular rash, seborrhea, skin discoloration, skin hyperpigmentation, subcutaneous nodule, and vesiculobullous rash.

Special Senses—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, catarrh, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urinary impairment, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, endometriosis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urethral stricture, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postmarketing Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after sexual withdrawal, hyperproliferation, and thrombocytopenia.

Overdose: Human Experience—As of December 1987, there were two deaths among approximately 39 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.83 mg/L; norfluoxetine, 1.10 mg/L; citalopram, 1.80 mg/L; temazepam, 3.00 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without sequelae.

PV 2472 DPP (11/78)

Additional information available to the profession on request from



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THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
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- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

HALDOL DECANOATE (HALOPERIDOL) INJECTION

Sustained protection
for the schizophrenic patient
with a single monthly dose

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (haptoglobinolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful.** However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias.** Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—Tardive dystonia, not associated with the above syndrome, has also been reported.** Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.**

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphopenia; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

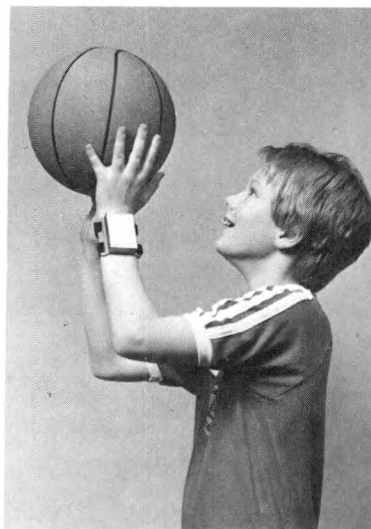
IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

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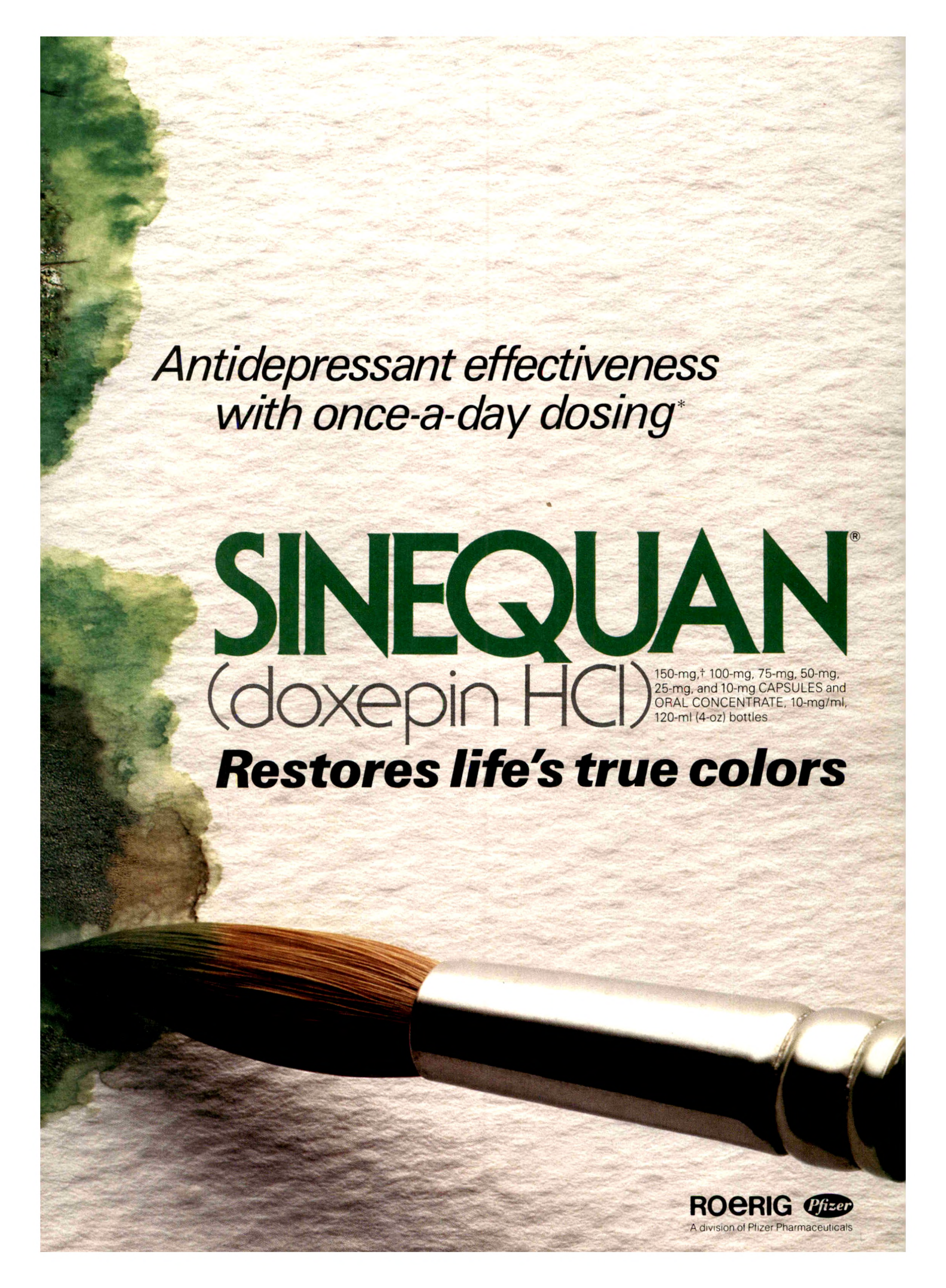


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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*Antidepressant effectiveness
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150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
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120-ml (4-oz) bottles

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
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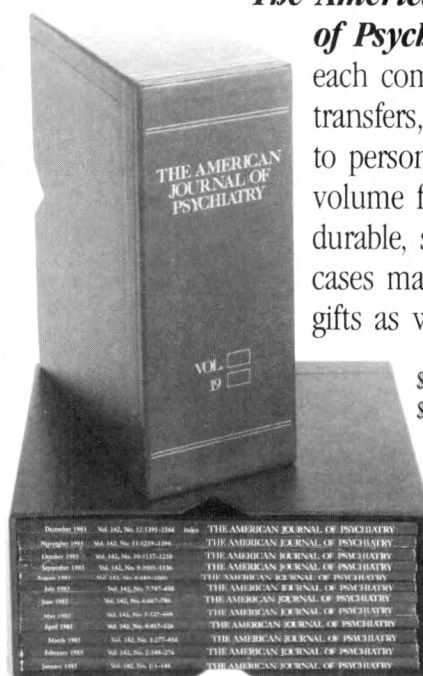
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Salus Populi

In the flurry of the clinical renaissance of interest in children with psychotic-like symptoms that occurred around 1940 (Bradley, Despert, and others), one clear description stood out. (Griesinger in 1845, Maudsley in 1897, and Emminghaus in 1887 all described children with patterns similar to those of adult mental patients; DeSanctis used the concept of *dementia precocissima* at the beginnings of this century.) The second volume of *The Nervous Child* carried both an introduction (1) and an article (2) regarding autism by Leo Kanner. Child psychiatry was thus introduced to a well-described, but prognostically bleak, syndrome.

So clear was the picture of autistic infants that secretaries in clinics could easily spot them. Yet the overwhelming nature of the care of these resistant children and the lack of positive affective response from them led their parents to push for exhaustive diagnoses as well as an ultimate pronouncement from the chief of the clinic.

Kanner's etiologic concept of the cold, intellectual, professional parents who confronted him fit the affective diagnostic philosophy of that day and set the tone for treatment measures best exemplified in Bettelheim's *The Empty Fortress* (3).

As with other entities, four decades of clinical progress have modified but not fully clarified the syndrome. In the 1940s and 1950s, physicians who saw such infants were often loath to diagnose them. Yet parental pressures, responding to the immediacy of the children's needs and their own frustrations when nothing seemed to work, were strong. Eventually these crystallized (as is our American wont) in the supportive National Society for Autistic Children.

Along with the elusivity of the etiology, the prevalence of the disorder has been unclear. Although autism is generally felt to be relatively rare, the obviousness of the clinical picture as well as the continuing demands of those who cared for the patients enhanced scientific interest in the condition. In the general range of emotional and mental disorders, autism stood out as a tangible subject for investigation and therapy. Like other clearly described but therapeutically puzzling syndromes, treatment followed the changing tides of clinical knowledge from analytic therapy through behavioral modification to a more biological approach, with various combinations thereof.

Perhaps the rarity, as well as the severity, of the disorder has sustained the prodigious medical, psychological, educational, and biological efforts that have been apparent in the last half-century. What is satisfying in "The UCLA-University of Utah Epidemiologic Survey of Autism: Prevalence" by Edward R. Ritvo, M.D., and his colleagues, published in this issue of the *Journal*, lies in the clarification of the prevalence. It takes diligence to use good public health measures to survey an entire state. The authors speak of it as an arduous project. The appropriate use of good epidemiologic methods is never an easy task.

Too often, those with a purely individual outlook eschew the methodologies used in public health practice. While we depend on the quality of such practices to sustain our health, we are more likely to take them for granted and focus our praise and concern on those who care for individual patients. Even we physicians attribute national improvements in health to the care of specific diseases rather than to the results of good preventive medicine.

This article thus confirms our expectations of a broader view from the Ritvo

group. They have long since pointed out that autism (despite Kanner's first patients) lacks correlation with parental education, occupation, race, or religion. It is, therefore, satisfying to see these factors once more confirmed—and on such a grand scale. Knowledge of this sort does not come easily. When clarification does come, it warrants praise for the use of proper methodology and the zeal of the investigators. Our understanding of many other syndromes would benefit, despite the difficulties involved, from such an approach.

Leo Kanner, a thorough investigator if there ever was one, would be pleased.

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HENRY H. WORK, M.D.

Dr. Work, formerly Deputy Medical Director, Professional Affairs, of the American Psychiatric Association, is Clinical Professor of Psychiatry, Georgetown University and George Washington University, Washington, D.C. Address reprint requests to him at 7001 Glenbrook Rd., Bethesda, MD 20814.

Four Studies of Mental Health Commitment

This issue of the *Journal* includes four careful and interesting studies related to mental health commitment. They illustrate the broad range of data-based studies and analyses being conducted in this important area. The most recent national data (1980) show that of 1,176,558 inpatient admissions, 26% were involuntary noncriminal commitments. More than 51% of admissions to state and county mental hospitals are, however, involuntary (noncriminal) (1). Despite these appreciable rates of involuntary admissions, many states are once more reevaluating their commitment criteria, with a handful moving away from civil libertarian reforms of the 1970s to embrace less restrictive commitment criteria.

The study by Hoge et al. is an empirical test of a theory, viz., Alan Stone's well-known proposal for commitment based on five conditions that justify a paternalistic, *parens patriae* approach. The major finding of Hoge et al. was quite unexpected. Compared to the present Massachusetts commitment approach that relies on patients' dangerousness, the Stone criteria might result in the hospitalization of a considerably smaller number of patients. Because of Stone's requirements—that patients exhibit major distress and be incompetent—many patients committed under the present Massachusetts dangerousness approach would not be committed under Stone's approach.

The Lidz et al. and Faulkner et al. studies are of commitment systems in operation in a particular jurisdiction. Lidz et al. found that clinicians' judgments of patients' dangerousness to others, inability to care for themselves, suicidality, and commitmentability show good, but by no means perfect, reliability. These authors analyze some of the reasons for discrepancies in clinicians' judgments.

The Faulkner et al. study illustrates a point well-known to clinicians. What happens to patients, the type of treatment they receive, may relate more to peculiarities of locale, setting, access to treatment, and administrative or fiscal contingencies than to statutory schema or required procedures that seemingly control.

Segal's analysis of cross-national data on mental hospitalization provides a broader perspective on commitment than the previous three studies. Using first-admission, age-specific, and gender-related data in three countries, including the United States, Segal argues that the differing rationales for commitment (need for treatment versus dangerousness) result in selection for hospitalization of a different patient population.

Uniting these studies is a lesson. To understand commitment, it is necessary to go beyond philosophy, jurisprudential concerns, or even dramatic case examples and, instead, to look at the commitment system in action. Preference for one set of commitment criteria, one set of procedures over another, should be based on fact and not only theory.

Do these studies suggest how commitment can be done better or whether, on the basis of their conclusions, we ought to make changes in the present commitment system? Here we are on less certain ground, in part because of limitations inherent in any single study and also because of interpretations that can be drawn.

The data presented by Faulkner et al. are the most clear-cut in terms of immediate systems implications. These authors demonstrate that profound effects can occur in commitment outcome because of the proximity of an evaluation facility and its ready availability to referring peace officers. When, for a period of time, contingencies favored hospitalizing patients locally rather than transporting them to a distant state hospital, dramatic reductions were found in the proportion of emergency commitments, the length of patient stays, and the number of subsequent hearings. Nevertheless, these apparently favorable outcomes were not sustained because of other fiscal contingencies. Based in part on studies similar to that of Faulkner et al., the recently promulgated Guidelines for Involuntary Civil Commitment of the National Center for State Courts (2) reinforce a similar conclusion and recommendation. Changing local administrative arrangements and providing better coordination can

profoundly affect the commitment system, even without statutory changes. Such is often not needed to provide better access to treatment or to protect patient rights.

The correlations that Lidz et al. demonstrate are good but not perfect. While Lidz et al. interpret their data to suggest that there is currently fair to good application of commitment standards, the findings they present are rather imperfect in one area. The reliability coefficient (R value) for clinicians' evaluations of patients' ability to care for themselves was rather low (0.44) for such an important judgment. This low correlation is of some concern, given that this type of passive danger to self is perhaps more rigorously defined in Pennsylvania law than elsewhere. This finding, as well as others on clinicians' uncertainties about the application of the least restrictive alternative doctrine, patients' rights to voluntary admission rather than commitment, and the handling of patient transfers within the commitment system, nicely demonstrates why there are discrepancies in commitment, even under a dangerousness type of law. The findings of Lidz et al. do, however, complement the above discussion. Training of clinicians, clarification of the meaning of statutes, and attention to confounding factors, rather than change of statutory language, may be the quickest or even the necessary road to reform.

The demographic data presented by Segal are striking. Countries that rely on the need-for-treatment approach seemingly select into treatment an older female population. The degree of dangerousness approach selects a younger male population. Segal argues, in a sophisticated way, about how to interpret these findings. Some caution is necessary, however. Segal's data on age and gender relate to all first admissions (voluntary and involuntary), not just admissions for committed patients. Thus the patterns presented reflect far more than commitment criteria—instead, a national preference for a particular type of patient or disorder. Segal also argues that commitment based on dangerousness affords less discretion to decision makers than does commitment based on need for care and treatment, thus constraining the population served. While recent elegant research by Segal et al. suggests this may be so (3–5), other findings suggest that clinician discretion is operative in the dangerousness area as well (6). Segal's findings are important and provocative. However, in practice, discretion may be operative under both need-for-treatment and dangerousness types of laws (7). In addition to statutory criteria, many factors affect who is committed. Whether the associations that Segal demonstrates have the causal significance that he attributes to them is less clear.

Finally, the study by Hoge et al. is a fascinating attempt to predict, through simulation, the effect of a change in commitment criteria before application. Hoge et al. are sophisticated, and they interpret their data cautiously. It probably cannot be known for certain what the impact of a return to paternalistic commitment would be without a real-life test. In theory, fewer patients, even more suitable patients, might be hospitalized. However, promulgation of the paternalistic approach to commitment (rather than patient dangerousness) would no doubt send a signal and be interpreted as societal sanction for more frequent or earlier hospitalization. This could create a climate in which a broader number of persons would be considered for hospitalization. Police, family members, and physicians might alter their threshold for considering hospitalization, with a resultant impact different from that which Hoge et al.'s study suggests, particularly if clinicians vary in their understanding or assessment of commitment criteria, as we can expect will occur.

Hoge et al. have done a valuable service in demonstrating the feasibility and effect of Stone's approach to commitment. What the accompanying articles in this issue of the *Journal* suggest is that reliance on changing commitment criteria to change commitment, without attention to the numerous other factors that affect commitment, would be shortsighted.

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LOREN H. ROTH, M.D., M.P.H.

Dr. Roth is Professor and Vice Chairman, Department of Psychiatry, and Director, Law and Psychiatry Program, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Roth, University of Pittsburgh, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

The Movement Toward Integrating the Psychotherapies: An Overview

Bernard D. Beitman, M.D., Marvin R. Goldfried, Ph.D.,
and John C. Norcross, Ph.D.

There is a growing tendency among psychotherapists to ignore the ideological barriers dividing schools of psychotherapy and to define what is common among them and what is useful in each of them. After a brief introduction the authors provide a short glossary of terms often associated with psychotherapy integration. They then characterize integrative-eclectic therapists, describe the forces fostering their emergence, and outline recurrent themes of the movement and points of contention within it. The authors hope to encourage clinical thinking about the less ideological approaches to psychotherapy and to advance the integrative movement, which is likely to influence psychotherapeutic practice for decades to come.

(Am J Psychiatry 1989; 146:138-147)

Psychotherapy systems appear and vanish with bewildering rapidity on the diffuse, heterodox scene in the United States. In 1959, Harper (1) identified 36 distinct systems of psychotherapy. In 1976, Parloff (2) discovered more than 130 therapies on the marketplace or the "therapeutic jungleplace." In 1986, Karasu (3) reported a count of more than 400 presumably different "schools" of psychotherapy. The proliferation of therapies has been accompanied by a deafening cacophony of rival claims. The result has been vari-

ously characterized as confusion, fragmentation, and discontent (4).

Sibling rivalry among theoretical orientations has a long and undistinguished history in psychotherapy, dating back to Freud. In the infancy of the field, therapy systems, like battling siblings, competed for attention and affection in a "dogma eat dogma" environment (5). Mutual antipathy, profound mistrust, and exchanges of puerile insults between adherents of rival orientations were very much the order of the day.

Amid this strife and bewilderment there slowly emerged a therapeutic "underground" (6). Although not associated with any particular school and not detailed in the literature, the underground reflected a growing openness to contributions from diverse persuasions as well as a nascent awareness that single schools had distinct clinical limitations. Adventure-some clinicians gradually, if unsystematically, began to use strategies that were efficacious without regard to their theoretical origin.

Of course, the notion of integrating various therapeutic approaches had intrigued mental health professionals for some time (7). However, it has been only within the past 10 or 15 years that psychotherapy integration has developed into a clearly delineated area of interest. This movement, by most accounts, has developed more as a cumulating climate of opinion than as an orderly scientific advance (8).

The last decade in particular has witnessed the stirrings of rapprochement and a decline in the ideological cold war. The debates across theoretical systems appear to be less polemical or at least more issue-specific. Clinicians of all persuasions have begun to acknowledge the inadequacies of any one system and the potential value of others.

The concomitant openness to contributions from diverse persuasions has given rise to many publications, organizations, and conferences. Specific systems of in-

Received Oct. 31, 1987; revision received March 28, 1988; accepted April 28, 1988. From the Department of Psychiatry, University of Missouri-Columbia; the Department of Psychology, State University of New York at Stony Brook; and the Department of Psychology, University of Scranton, Pa. Address reprint requests to Dr. Beitman, Psychiatry Clinic, University of Missouri-Columbia Hospital and Clinics, Columbia, MO 65212.

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tegrative and eclectic practice (9–13), influential anthologies (4, 14–16), and compilations of prescriptive treatments (17, 18) have flourished. An international journal (*Journal of Integrative and Eclectic Psychotherapy*) and several series of articles devoted to psychotherapy integration have appeared in the last decade. Two interdisciplinary and nonideological organizations—the Society for the Exploration of Psychotherapy Integration and the International Academy of Eclectic Psychotherapists—also exemplify the spirit of open inquiry and growing collaboration.

This article is designed to provide an overview of the movement toward the integration of the psychotherapies. It will not address the combination of psychotherapy and psychopharmacology (19, 20) nor the synthesis of such therapeutic formats as individual, family, or group therapy. We will begin with a short glossary of terms often associated with integrative movements. We will then characterize integrative-eclectic therapists and outline the forces fostering their emergence. Several recurrent themes and points of contention follow.

A SHORT GLOSSARY

The terminology relating to the psychotherapy integration movement has been applied inconsistently and indiscriminately. This semantic disarray has fostered conceptual confusion. In this section, we briefly review the definitions of and distinctions among these terms in an effort to clarify our thinking and to enhance the consistency of our vocabulary.

Rapprochement. According to Webster's *Ninth New Collegiate Dictionary*, "rapprochement" refers to the "establishment of or state of having cordial relations." This term denotes an earlier developmental stage than mature theoretical integration in that cordial relations typically precede incorporation.

Convergence. This is the tendency to grow alike, to develop similarities in form. Many observers (15, 21–24) have noted increasing confluence of attitudes and practices among the psychotherapies. Behavior therapy, for instance, has largely regained its "mind" and has become far friendlier to the cognitive concepts of psychoanalysis and to the affective experiences of humanistic-expressive therapies (24). "Convergence" refers, however, to emerging similarities of distinct orientations rather than to their integration per se.

Eclecticism. This is a vague and nebulous term, with connotations ranging from "a worn-out synonym for theoretical laziness" to the "only means to a comprehensive psychotherapy" (25). In some corners eclecticism is prized as complex, relativistic thinking by people united in their respect for the evidence. In other corners, it connotes undisciplined subjectivity and muddle-headedness (26). Indeed, it is surprising that so many clinicians admit to being eclectic in their work, given the negative valence the term has acquired (27).

Apart from its connotation, the use of "eclecticism"

has increasingly been restricted to the technical, atheoretical synthesis of clinical methods. Lazarus (12, 28, 29), the most eloquent proponent of technical eclecticism, emphasized the distinction between the theoretical eclectic and the technical eclectic. The theoretical eclectic draws from diverse systems that may be epistemologically and ontologically incompatible, whereas the technical eclectic uses procedures drawn from different sources without necessarily subscribing to the theories that spawned them. We will employ "eclecticism" in the technical, atheoretical sense advanced by Lazarus.

Integration. Although "eclecticism" is certainly one component of the integration of psychotherapy in that it integrates clinical methods from diverse sources, the term "integration" has come to acquire a more theoretical meaning (30, 31). "Integration" commonly denotes the conceptual synthesis of diverse theoretical systems. "Eclecticism," by contrast, is atheoretical but empirical in pragmatically applying what already exists. "Integration" is more theoretical than empirical in creating something "new": a superordinate umbrella, coherent theoretical gestalt, metatheoretical framework, or conceptually superior therapy (32).

Other descriptive terms have been proposed as alternatives or replacements for the foregoing. These include "creative synthesis," "metamodeling," "comprehensive therapy," "prescriptive counseling," and "differential therapeutics." Each term has a slightly altered emphasis, but all generally denote a trend toward a more consensual and comprehensive framework.

INTEGRATIVE-ECLECTIC PSYCHOTHERAPISTS

Eclecticism has emerged as the modal theoretical orientation of contemporary mental health professionals. Across all disciplines, between one-third and one-half of American psychotherapists disavow an affiliation with a single therapeutic tradition, preferring instead the label of eclectic. This holds true for psychiatrists (33, 34), psychologists (35, 36; unpublished 1988 manuscript of J.C. Norcross et al.), and clinical social workers (34, 37). Interestingly, even surveys of clinicians belonging to behavioral and humanistic organizations reveal sizable percentages of respondents who align themselves with eclecticism: 42% of behavioral clinicians (38) and 31% of humanistic clinicians (39).

The existing research has not delineated any consistent differences between those psychotherapists who identify themselves as eclectic and those who identify themselves as noneclectic, with the exception of clinical experience (39–41). This research has indicated that clinicians ascribing to eclecticism tend to be older and more experienced. Conversely, inexperienced therapists are more likely to endorse exclusive theoretical orientations. Reliance on one theory and a few techniques may be the product of inexperience; put another way, with experience comes diversity and flexibility.

Eclecticism is approached from a multitude of pathways. Garfield and Kurtz (42) found that approximately 40% of eclectic respondents had not previously adhered to a particular theoretical perspective, whereas 50%–60% indicated that they had. Of those with previous theoretical allegiances, the largest shift occurred from psychodynamicism and psychoanalysis to eclecticism. Norcross and Prochaska (31) found that one-half of eclectic psychologists with a previous alliance were formerly in the analytic tradition, and Jayaratne (43) found that one-half of eclectic social workers with a previous alliance were also formerly in the analytic tradition. Next most common for both groups were the behavioral and client-centered orientations.

There appears to be an emerging preference for theoretical synthesis (integration) as opposed to technical synthesis (eclecticism). In the 1970s, 47% of eclectic therapists characterized their clinical practice as pragmatic-technical eclecticism (42), whereas 34% did so in a 1980s sample (31). Concomitantly, 27% of the respondents in the 1970s combined two theories or amalgamated aspects of multiple theories (42), whereas 39% indicated that they did so in the 1980s (31).

WHY INTEGRATION NOW?

A historical perspective of psychotherapy integration (7) has persuasively demonstrated that the stirrings of rapprochement have always been with us but have been actualized and organized into a coherent movement only recently. The unprecedented growth in integrative psychotherapies over the past decade leads one to inquire, Why now? What is there in our socioeconomic environment or the field's maturation that has intensified the spirit of open inquiry?

At least six interacting, mutually reinforcing factors have fostered the advancement of psychotherapy integration in the past decade (4, 7, 44).

1. *Proliferation of therapies.* In describing the genesis of scientific revolutions, Thomas Kuhn (45) indicated that the abandonment of any given paradigm is ordinarily preceded by a period of crisis. This crisis is characterized by the open expression of discontent about the current state of affairs and by the proliferation of different orientations. The field of psychotherapy, it would appear, is currently experiencing such a crisis (46).

The field has been staggered by too many choices and fragmented by future shock. Which of the more than 400 therapies should be studied, taught, or bought? No single theory has been able to corner the market on validity or utility. The search for a more unified and comprehensive paradigm has thus become a prime motivation for both eclectic and integrative psychotherapists.

2. *Inadequacy of single theories.* A related factor is the growing consensus that no one approach is clinically adequate for all problems, patients, and situa-

tions. Clinical realities have come to demand a more flexible, if not integrative, perspective. Psychotherapy, as a result, has entered a period of intense self-examination in which the failures of our pet theories are reappraised and their limitations realized. The integration movement, to some extent, reflects dissatisfaction with single approaches. A survey of self-designated eclectic and integrative clinicians (42) revealed that their alignment is motivated in part by disillusionment with single-therapy systems.

3. *Equality of outcomes among therapies.* A third reason for the recent surge toward integration is the general inability to show that one therapeutic approach is clearly superior to any other in manifest outcome (47–49). Despite a notable increase in both the quantity and quality of psychotherapy research, there are few conditions in which a given therapy system leads to differential effectiveness. With few exceptions, there is little compelling evidence to recommend the use of one form of psychotherapy over another in the treatment of specific problems. Borrowing a phrase from the Dodo bird in *Alice in Wonderland*, Luborsky et al. (50) wryly concluded that “everybody has won and all must have prizes.”

A paradox has emerged from the equivalence conclusion: there is no differential effectiveness despite technical diversity (51). A number of reasons for this paradox have been advanced, notably the lack of specificity of outcome measurement, the poor integrity of treatments, and the elucidation of common core factors in the therapist, client, or alliance. The two most common suggestions for resolving the paradox seem to be a specification of factors common to successful treatments (52) and a synthesis of useful concepts and methods from disparate therapeutic traditions (53).

4. *Resultant search for common components.* The identification of common change processes or therapeutic factors has been called the most important psychotherapy trend in the 1980s (54). Strupp (55) has noted that the important advances in psychotherapy research have resulted from better conceptual analyses of basic processes operating in all forms of therapy rather than from premature comparisons of techniques. This observation stems from the emerging view that the commonalities in all forms of therapy are far more impressive than their apparent differences.

A transtheoretical analysis of prominent psychotherapy systems (56) demonstrated how much therapeutic systems agree on the processes producing change while disagreeing on the content to be changed.

Frank (57) posited that all psychotherapeutic methods are elaborations and variations of age-old procedures of psychological healing. The features that distinguish psychotherapies from each other, however, receive special emphasis in our pluralistic and competitive society. Since the prestige and financial security of psychotherapists hinge on their particular approaches being more successful than those of their rivals, little attention has been traditionally accorded the identification of shared components (4).

Frank (47, 57, 58), among others, has argued that therapeutic change is predominantly a function of factors common to all approaches. For Frank, these include an emotionally charged and confiding relationship, a healing setting, a rationale or conceptual scheme, and a therapeutic ritual. For Garfield (11), these common factors entail the relationship, catharsis, explanation, reinforcement, desensitization, information, and time. Similarly, Karasu (3) identified three nonspecific change agents that all therapy schools share: affective experiencing, cognitive mastery, and behavioral regulation. These authors have noted that features shared by all therapies account for an appreciable proportion of clinical improvement, and psychotherapy outcome research (59) has generally substantiated this claim.

5. *Emphasis on patient characteristics and the therapeutic relationship.* Psychotherapy researchers have come to recognize that the powerful determinants of therapeutic success lie in the personal qualities of the patient and the therapist and in the interaction between them. The particular clinical method appears to have little differential effect. Meta-analytic studies (49, 60, 61), for example, indicate that only 10%–12% of outcome variance is generally accounted for by technique variables. In substantial concurrence, a panel of psychotherapy experts (62) estimated that one-third of treatment outcome is due to the psychotherapist but two-thirds is attributable to the patient. Echoing the consensus on the issue, Bergin and Lambert (63) concluded, "We believe . . . that the largest variation in therapy outcome is accounted for by preexisting client factors, such as motivation for change, and the like. Therapist personal factors account for the second largest proportion of change, with technique variables coming in a distant third" (p. 180).

Consequently, it would appear that singular attempts to improve techniques within one orientation would have a negligible effect on therapeutic outcome. Beutler (64) has noted the irony of devoting 80% of the psychotherapy literature to specific technologies and procedures, which account for about 10% of the change.

Instead, our efforts might be more profitably expended in tailoring the therapeutic relationship and clinical method to the patient. To the extent that there are some specific technique effects (and refined research may discern still more), treatment success can be maximized by altering the therapist's stance and operations to the patient's presenting problem, interpersonal style, personality configuration, readiness to change, and related variables. To the degree that clinicians are able to modify and enlarge their practices to fit the patient's needs, the benefits are potentiated. This is one of the distinguishing characteristics of the integration movement: prescriptive treatment based primarily on patient need and empirical evidence rather than on theoretical predisposition (17).

6. *Sociopolitical contingencies.* The movement toward integrating the psychotherapies is one adaptive

response to social, political, and economic influences. There are at present mounting pressures from insurance companies, government policy makers, consumer groups, and judicial officials for accountability. Third parties and the public are demanding crisp and informative answers regarding the quality, durability, and efficiency of psychosocial treatments (65). Until recently the field has had the luxury of functioning within a culture of individual professional freedom. Clinical services had been in steady demand in the marketplace, generally oblivious to economic forces and sociopolitical realities. However, the shrinking job market, increased competition, and diminishing public support portend a future discontinuous with our expansive past (66).

Without some change from the field, psychotherapists stand to lose prestige, customers, and money. These sociopolitical considerations have us increasingly pulling together rather than apart. Mental health professionals report that political and economic changes have led them to work harder, to be more creative, and to adjust their treatments to meet the needs of their clients (67). Intertheoretical cooperation and the search for a unified psychotherapy paradigm represent attempts to respond to these sociopolitical forces. As the external demands escalate, so too will the spirit of open inquiry and psychotherapy integration.

RECURRENT THEMES

In a historical analysis of previous attempts to integrate the psychotherapies, Goldfried and Newman (7) identified issues that have repeatedly emerged over the past half century. Such recurrent themes include the complementary nature of different therapeutic approaches; the advantages of identifying interactions among cognition, affect, and behavior in patients; the importance of an empirical foundation on which therapies may be based; the need for a common language with which to engage in dialogue across different orientations; the need to arrive at a set of therapeutic principles that can account for commonalities across different orientations; and the view of therapy as involving certain common phases or stages. As the topic of therapeutic integration has moved from being a latent concern to a more clearly defined area of interest, clinicians and researchers have started to devote increasingly more attention to each of these themes. The sections that follow describe some of these considerations.

Complementary Nature of Different Orientations

Clinical experience and research findings alike lead us to the conclusion that each therapeutic orientation has its share of clinical failures and that none is consistently superior to any other (51). Such findings have stimulated many workers in the field to consider the possibility that contributions from orientations other than their own might be fruitfully employed. In es-

sence, the weakness of any one orientation might be complemented by another's strength. This notion has been articulated by Pinsof (68), who described an integrative problem-centered therapy as one that "rests upon the twin assumptions that each modality and orientation has its particular 'domain of expertise,' and that these domains can be interrelated to maximize their assets and minimize their deficits" (p. 20).

In considering the potential benefits and liabilities of an integrative approach, Messer and Winokur (69) indicated that patient variables may play a particularly important part in determining the most appropriate therapeutic intervention. Thus, a verbally limited patient with little skill at introspection may be less likely to benefit from psychodynamic treatment but may, instead, show greater gains with an action-oriented, behavioral intervention. Like Wachtel (6, 70), Messer and Winokur further argued that both action and insight might be effectively used in any given case, particularly when insights are translated into action, which can in turn further enhance awareness.

Consistent with this thesis, Fensterheim (71) suggested that a psychoanalytic style may be used to develop hypotheses about ways patients organize their perceptions of the world and to select the most relevant behavior patterns that are in need of change. Having done so, however, a behavioral approach may then be more appropriate in helping to actually facilitate behavior change.

Another way in which the complementarity between psychodynamic and behavior therapies may be implemented has been noted by Messer (72), Rhoads (73), and Salzman (74). It has been suggested that there will be times when a behavioral approach may be called for to help a patient cope with some debilitating symptom at the outset of therapy. Having gained the patient's trust and cooperation, the therapist may more readily be able to use a psychodynamic approach to explore long-standing problems that have contributed to the initial complaint. By achieving insight through this second phase of treatment, the therapist may then return to a behavioral orientation to help patients develop more adaptive behavior patterns.

Interaction of Cognition, Affect, and Behavior

In the most general sense, different therapeutic orientations have tended to focus on different aspects of a patient's functioning. Thus, psychodynamic therapy has tended to deal with awareness, experiential therapy with emotionality, and behavior therapy with the patient's action patterns. The emphasis of such therapists as Lazarus (75) on "multimodal" therapy has underscored the importance of dealing with the interaction among these different components of a patient's functioning. Integrative therapists, such as Driscoll (76), have raised the question, Shouldn't the choice to concentrate on one component more than others be a function of patient characteristics instead of the therapist's training background?

In an article that draws a parallel between interpersonal therapy and cognitive-behavioral approaches, Safran (77) suggested that Sullivanian concepts can supplement the cognitive-behavioral approach by providing a framework within which "hot" information processing occurs in an emotional and interpersonal context. Based on experimental data and models of information processing, Greenberg and Safran (78) proposed a way of conceptualizing the integration of emotion and cognitive processes within a single approach to therapy.

An Empirically Based Therapy

Clinicians and researchers alike have long called for the development of a theory of therapy that would have a strong empirical base. Strupp (79) has emphasized that therapies must be testable, so that independent observers can specify what is going on clinically, communicate to others about such phenomena, and ultimately reach some consensus as to whether therapeutic change has in fact occurred. Although many modern workers in the field have reaffirmed this position and it is generally agreed that psychotherapy is effective in producing change (48), little empirical work has been done to specify the actual principles that underlie the change process. There has been considerable speculation about such principles on the basis of what different therapists say they do, but much less is available that is based on direct observations of what therapists actually do (46). It has been suggested (80) that a workable methodology is needed in order to study the common principles of therapeutic change and that such research efforts may best be found in the area of psychotherapy process research.

Need for a Common Language

It should come as a surprise to no one that each of our therapeutic orientations has its own unique set of jargon which, although facilitating communication within a school, prevents dialogue across orientations. Such problems in communication are reflected not only in the difficulty one has in understanding concepts from another orientation but also in the emotional barriers to listening that occur when one hears certain terms associated with another orientation (e.g., "extinction," "self-actualization," and "transference").

At an NIMH workshop on research in psychotherapy integration (81), it was noted that the language of psychotherapy may be used for four different purposes: 1) to enhance communication within a particular school, 2) to retrieve basic research findings from the literature, 3) to engage in dialogue with colleagues of different orientations, and 4) to carry out comparative psychotherapy process research. To communicate with colleagues that subscribe to our own orientation, the use of jargon typically affords us a relatively convenient and efficient method of communication—either with each other or with the psychotherapy lit-

erature that is derived from a particular school of thought. However, basic research on human functioning and the change process is rarely couched in the jargon of any of our therapeutic orientations. Consequently, a translation is needed between the jargon of our particular therapeutic school and the language systems used in basic research on human functioning (cognitive psychology and social psychology, for example). The NIMH workshop participants suggested that in engaging in dialogue across orientations, ordinary or natural language (everyday English) would stand the best chance of allowing for cross-theoretical conversation. Finally, a psychotherapy research language was suggested, which would allow the incorporation and translation of the concepts from various theoretical orientations into an operationalized system that was neutral with regard to each of the separate schools. Creating such a language for psychotherapy process research would enable us to identify points of convergence and points of contention as they occur within different therapy interventions.

The Search for Common Therapeutic Principles

Goldfried (53) has suggested that a particularly fruitful way of determining common therapeutic principles is by focusing on a level of abstraction somewhere between theory and clinical technique. This intermediate level of abstraction, referred to as a clinical strategy, may be thought of as a heuristic tool that implicitly guides the efforts of experienced therapists. Goldfried (53) argued,

To the extent that clinicians of varying orientations are able to arrive at a common set of strategies, it is likely that what emerges will consist of robust phenomena, as they have managed to survive the distortions imposed by the therapists' varying theoretical biases. (p. 996; author's italics)

Although there have been no empirical studies of common clinical strategies based on direct observations of therapy sessions, a review of the available literature (13, 46) reveals a number of potential similarities. Among these are the initial expectations that therapy may be helpful, the patient's participation in a therapeutic relationship, the opportunity to obtain an external and/or objective perspective on one's problems, the encouragement of corrective experiences, and the opportunity to engage in repeated reality testing. Even though the specific clinical procedures used to implement each of these strategies may conceivably vary from orientation to orientation, the strategies themselves nonetheless represent common threads.

Stages of Psychotherapy

One of the common heuristic tools used by therapists across orientations is the notion that psychotherapy proceeds in stages. Patients must be engaged in therapy; patterns of dysfunction must be elucidated;

these patterns must then be altered in some beneficial way; termination then follows (9, 10, 13). These stages may be defined by their objectives: engagement, pattern search, change, and termination (9). Some evidence suggests that change may be divided into three substages: giving up the old pattern (or patterns), initiating the new pattern, and maintaining the new pattern (9). Several investigators have examined the critical elements of the engagement process, including the patient's and therapist's perceptions of each other, the therapist's techniques, and the patient's motivation (82). Future research is likely to elucidate the optimal approach to dysfunctional patterns and the management of the substages of change.

POINTS OF CONTENTION

At the 1932 annual meeting of the American Psychiatric Association, Thomas French (83) stood before his audience and presented his thoughts on the relationship between psychoanalysis and Pavlovian conditioning. Horrified by French's attempt at rapprochement, Myerson (84) confessed,

I was tempted to call for a bell-boy and ask him to page John B. Watson, Ivan Pavlov, and Sigmund Freud while Dr. French was reading his paper. I think Pavlov would have exploded; and what would have happened to Watson is scandalous to contemplate, since the whole of his behavioristic school is founded on the conditioned reflex . . . Freud . . . would be scandalized by such an rapprochement made by one of his pupils, reading a paper of this kind. (p. 1201)

The latent theme of psychotherapy integration has continued over the past half decade or so, and staunch supporters of specific schools of thought have voiced their strong opposition to such trends. These arguments have typically been presented in passing and have usually been of the "my-school-is-better-than-yours" variety. As this latent theme has developed into a clearly articulated area of interest—indeed, movement—reservations about integration have become more explicit (85–87). Supporters and critics of the integration movement have begun to engage in open dialogue (14, 88), and certain points of contention have been debated, including the conflicting perspectives on reality held by differing schools, the role of the unconscious, the importance of transference, and the goals of psychotherapy itself.

Conflicting Perspectives on Reality

Messer and Winokur (69) and Yates (87) have argued that in the light of the differing world views taken by psychodynamic and behavior therapists, little hope exists for rapprochement between these orientations. Messer and Winokur (69) described a behavioral approach as being consistent with a "comic" view of human functioning, reflected in the belief that happi-

ness can be obtained in one's life by identifying and removing environmental barriers. By contrast, psychoanalytic therapists assume a "tragic" view, which recognizes and accepts some of the limitations inherent in the human condition. Similarly, Yates (87) characterized the behavioral approach as emphasizing realism, objectivity, and "extraspection," in marked contrast to the psychoanalytic perspective of idealism, subjectivity, and introspection. In acknowledging that such differing world views do indeed exist, however, several theorists (89-91) have suggested that these differences in philosophy are precisely what makes psychotherapy integration interesting, in that it brings together the strengths of the different orientations.

The Role of the Unconscious

One of the basic differences that has existed between psychodynamic and behavioral approaches to therapy has been that of "the unconscious." Indeed, the essence of therapeutic change from a psychodynamic point of view has traditionally focused on underlying conflicts and needs of which the patient had little or no awareness, whereas a behavioral approach has typically emphasized the development of alternative behavior patterns and alteration of interfering environmental factors.

Although the concept of the unconscious appears to represent an irreconcilable point of incompatibility between psychodynamic and behavior therapy, this is the case only if one compares classical psychoanalysis and radical behavior therapy. As emphasized by many writers (6, 11, 77, 92-94), today's psychodynamic therapists have begun to recognize the importance of conscious thoughts, action, and environmental factors, and behavior therapists' recognition of cognitive factors has led them to accept the importance of "implicit" thoughts.

Meichenbaum and Gilmore (94) suggested that all therapies deal either directly or indirectly with the patient's hypothesized cognitive structures. These authors maintain that the psychodynamic goal of making the unconscious conscious parallels the cognitive-behavioral therapist's attempt to have patients identify automatic assumptions about themselves and others. To be sure, there are theoretical differences between these two views of unconscious processes. For example, the psychodynamic view maintains that the unconscious reflects a basic motivational system within the individual, whereas the cognitive-behavioral view adopts a more nonmotivational, information-processing conceptualization. Nonetheless, we seem to be witnessing a most important convergence between what have traditionally been opposing views of this clinical phenomenon.

The Importance of Transference

Another key concept that has served as a barrier for the integration of psychodynamic and behavior ther-

apy is that of the existence and function of transference. In addressing this issue, Gill (95) expressed doubts that classical psychoanalysis, which requires a uniquely ambiguous and restrained analytic stance, could ever be integrated with any intervention approach in which the therapist is more directive. Gill acknowledged, however, that this basic incompatibility does not necessarily exist between psychoanalytically oriented therapy and other approaches.

In conceptualizing the therapeutic interaction from a more Sullivanian point of view, Wachtel (6) maintained that the therapist can never really be the total "blank screen" presumably required for the development of a transference reaction. As participant and observer, the therapist "is as much a part of the context if he is silent and invisible as if he is face to face with the patient and overtly discernibly responding to him" (p. 69). Such a broad conceptualization of the therapeutic context, Wachtel argued, allows one greater freedom to intervene with procedures that might be more directive in nature.

Viewing transference from a cognitive-behavioral vantage point, Arnkoff (96) noted that certain similarities exist between psychodynamic and cognitive-behavioral approaches in the use of the therapeutic relationship. She suggested that there may be instances in cognitive-behavioral therapy when it is most relevant to focus on the relationship as it is occurring within the session itself. This observation has also been made by Goldfried and Davison (97) and Goldfried (98), whose depictions of cognitive-behavioral therapy allow for the possibility that the therapeutic relationship offers a sample of the patient's relevant thoughts, emotions, and behavior, thereby affording the opportunity for an "in vivo" intervention. The primary difference between the use of the therapeutic relationship in these two therapeutic approaches appears to be more the relative emphasis placed on this therapeutic change procedure rather than its existence.

Goals of Therapy

Beutler (10) has suggested that different therapeutic orientations probably do not dictate the specific interventions used so much as they determine the therapeutic goals to pursue. In arguing for the incompatibility of different therapeutic approaches, Yates (87) maintained that the differences in goals are a function of basic philosophical differences across therapeutic viewpoints. Thus, a behavioral therapist might emphasize the need to change specific behaviors and perceive a patient's sorrow as a negative emotion to be eliminated. A psychoanalytically oriented therapist, on the other hand, might choose to focus more directly on the sorrow and, construing it as a natural reaction to an unfortunate life circumstance, would pursue the goal of helping patients to experience, work through, and finally accept certain losses.

Wachtel (6) related potential differences in therapeutic goals set by behavioral and psychodynamic thera-

pists as a function of their conceptualizations of the patient's problem. From a behavioral point of view, problems are more likely to be construed as reflecting the individual's difficulty in attaining certain socially acceptable aims in life. Psychodynamic therapists, by contrast, view a patient's problem as reflecting conflicting needs and wants, some of which may be socially unacceptable. Consequently, the behavioral therapist's goal would be to assist patients in making changes in either themselves or their environment that might more readily allow them to obtain their objectives, whereas a psychodynamic therapist would primarily work with helping patients to develop an understanding of the internal conflicting factors. Neither is necessarily more correct, Wachtel pointed out, and there is nothing to prevent either the behavioral therapist or the psychodynamic therapist from pursuing both goals.

Messer (24) has dealt at length with the complementary nature of therapeutic objectives outlined within psychodynamic and behavioral points of view. Noting that the visions of reality have begun to change among practicing psychodynamic and behavioral therapists, he outlined how each therapeutic orientation might fruitfully expand its range of therapeutic goals in actual clinical practice. Messer (24) fully acknowledged that not all therapists would be willing to engage in this integrative effort, but that

there are many therapists of both orientations who undoubtedly will welcome the kind of change occurring in each therapy. For them, the mutual influence of one therapy on the other, the convergence of certain perspectives, and the particular shift of visions and values that this entails constitute a creative challenge both to the theory of each therapy and to its practice. (p. 1270)

FUTURE DIRECTIONS

The integrative movement appears to be gaining momentum and is likely to be the *Zeitgeist* of the next several decades of psychotherapy research and practice. Unsubstantiated theories about the psychotherapeutic process will grudgingly give way to solidly grounded concepts to which the different approaches will make their various contributions. The great charismatic leader proclaiming the right and true path is likely to gain fewer constituents as psychotherapy becomes increasingly more pragmatic. New ideas will be welcomed as contributions rather than quantum leaps into new and startling territory. Trainees, we hope, will be less ideologically programmed and will be taught to recognize the value of each of the many approaches as well as the inevitable influence of their own personalities on the process (99). Ideally, consumers of psychotherapeutic services will be shown clearly just what it is they are receiving and thereby be able to make better judgments about their reasons for choosing this form of assistance.

A number of formidable obstacles confront this movement as it grows to represent a substantial number of practicing and research psychotherapies (100). For example, can comprehensive frameworks and/or a common language be developed that are acceptable to diverse audiences? Can we overcome the interprofessional bickering and partisan zealotry that continue to restrain psychotherapeutic evolution? Will integrative therapists be able to effectively train neophyte clinicians in multiple approaches and integrative perspectives? Will future research demonstrate the utility of integrative concepts and strategies? Will the movement generate information for the practicing clinician that will improve his or her ability to decide what to do, when, and with which patient? Will it be necessary to develop not only a superordinate clinical theory but also integrative theories of personality and psychopathology? We are witnessing an exciting development in the history of psychotherapy. The future holds the answers to its durability and significance.

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A Neuroanatomical Hypothesis for Panic Disorder

Jack M. Gorman, M.D., Michael R. Liebowitz, M.D., Abby J. Fyer, M.D.,
and Jonathan Stein, B.A.

Anxiety disorders, the most common psychiatric conditions in the United States, have generated a great deal of research and scientific debate. Panic disorder, the best-studied anxiety disorder, is often believed to be either a biological disease or a psychological disease. The authors present a neuroanatomical model of panic disorder that attempts to reconcile these views. The model locates the three components of the disease—the acute panic attack, anticipatory anxiety, and phobic avoidance—in three specific sites of the CNS: the brainstem, limbic system, and prefrontal cortex, respectively. The authors suggest experiments to test their model.

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The striking increase over the last 5 years in research interest into anxiety disorders has been made even more explosive by the National Institute of Mental Health Epidemiologic Catchment Area Program survey (1) finding that these conditions are the most prevalent psychiatric illnesses in the United States. With all of this attention, the study of one anxiety disorder—panic disorder—has become a microcosm of many of the classic controversies surrounding psychiatric research.

So-called biological psychiatric researchers have developed hypotheses for the generation of panic attacks and panic disorder that invoke putative abnormalities in brain neurochemistry, metabolism, genetics, and receptor physiology. These scientists generally favor psychopharmacological treatments of panic disorder.

On the other hand, so-called behavioral researchers,

with an impressive data base to speak from, point to etiologies based on learning theory and cognitive psychology. These scientists generally favor behavioral and cognitive therapies, saying that drug treatments are either ineffective or produce only symptomatic relief which disappears once the medication is discontinued.

Somehow, it is widely believed that panic disorder must be either a “biological” disease or a “behavioral-cognitive” disease. If it is a biological disease, then drug treatment is thought to be the appropriate treatment, with psychotherapy only an adjunct to ensure that the patient continues to take medication properly. If it is a behavioral-cognitive disease, then behavioral-cognitive psychotherapy is deemed the treatment of choice, with drugs reserved for short-term symptomatic relief for particularly difficult cases.

There are innumerable theoretical and practical consequences of this kind of debate. For one, the nature of the term “biological” seems grossly misused. Ultimately, every aspect of human behavior must have a biological basis; the action of neurons in the brain controls all such functions. Consequently, no theory of a psychiatric disorder can possibly be complete without reference to various aspects of the neurochemistry and neuroanatomy involved.

By the same token, it is inconceivable that anxiety disorders do not substantially involve disordered cognitions and learning. These complex illnesses occur in patients who usually function well otherwise but develop complicated rationales for and reactions to the anxiety symptoms that bombard them. No etiological hypotheses of panic disorder should be considered complete that do not include these aspects.

Practically, patients are increasingly perplexed by divisions in the field about appropriate treatment. They can read exaggerated claims in newspapers and magazines by supposed experts claiming that various drugs or psychotherapies are the best remedy. Unlike the approach to other medical conditions, the patient with panic disorder can never be sure that he or she is receiving a widely recognized and accepted treatment of choice. Such lack of firm ground can be highly distressing for the anxious patient.

Research into panic disorder now permits us to speculate about how the various competing views might be merged into a more useful and comprehensive theory. Although obviously hypothetical, our attempt is based on work in both the biological and behavioral spheres.

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This hypothesis is presented for two reasons. First, it may serve as a basis for future "hypothesis-generated" research. Second, it forms a rational way to explain to patients the nature of the illness and approaches to treatment; this explanation is neither doctrinaire nor vague.

The hypothesis we wish to propose may be summarized as follows. There are three distinct components of the illness panic disorder—the acute panic attack, anticipatory anxiety, and phobic avoidance. These three clinical phenomena arise from excitation in three distinct neuroanatomical locations, respectively: the brainstem, limbic lobe, and prefrontal cortex. Reciprocal innervation among nuclei in these three centers explains the genesis of the disease and its clinical fluctuations over time.

After a brief description of the three components of the disorder, we will present evidence for the neuroanatomical localization and pathways that are specifically involved.

THE PHENOMENOLOGY OF PANIC DISORDER

The neuroanatomical hypothesis presented here is based on one specific way of describing the clinical presentation and course of panic. This description was probably first articulated by Freud (2): "In the case of agoraphobia . . . we often find *the recollection of an anxiety attack*; and what the patient actually fears is the occurrence of such an attack under the special conditions in which he believes he cannot escape it."

Klein (3) has formulated a three-part phenomenological model for panic disorder. The acute panic attack is the keystone of this model, characterized by sudden and spontaneous, crescendo-like onset of autonomic symptoms and a subjective sense of dread. These attacks last between 10 and 30 minutes in most instances, and then the patient returns to baseline functioning.

The second feature is anticipatory anxiety. Here, the patient begins to worry that an attack will occur again. Rather than returning to baseline after each attack, the patient now exists in a more chronic state of anxiety, always anticipating the onset of an attack.

Finally, a subset of patients with panic disorder develops the third part of the illness—phobic avoidance. These patients become so fearful of having attacks that they shun situations in which help cannot be easily obtained once the acute attack strikes. It is not generally understood why some patients develop phobias and others do not, or why some patients have only limited phobic avoidance—i.e., they avoid a few situations and this has no substantial impact on their usual functioning—while others become virtually house bound.

The crucial aspect of this description is that phobic avoidance in the patient with agoraphobia is held to be secondary to the fear of having a panic attack. This is somewhat controversial because the notion that panic

attacks cause agoraphobia is disputed by some theorists, who are supported by one finding from the Epidemiologic Catchment Area Program study (4) indicating a population of agoraphobic patients who failed to give previous histories of panic. Nevertheless, most patients with agoraphobia studied in research settings had panic attacks before becoming phobic (5–7). These data come from both "biological" and "behavioral" laboratories.

It is conceivable, as will be pointed out later in this paper, that our theory could be applied to agoraphobic patients without previous panic attacks, if such patients actually exist. It mainly applies, however, to those patients who have had acute panic attacks before developing phobic avoidance.

By the time the patient with panic disorder presents to the clinician, the three phases of the illness—i.e., panic attacks, anticipatory anxiety, and phobic avoidance—are likely to be present in various mixtures. Additionally, the patient probably has developed his or her own explanation for what generates various symptoms, manifests demoralization secondary to the functional impairment caused by the disease, and has substantial interpersonal difficulties. Studies have indicated that up to 70% of patients with panic disorder develop depression (7, 8) and that there may be a genetic link between panic disorder and depression (9).

It is little wonder, then, that much "heterogeneity," both biological and nonbiological, turns up when the patient with panic disorder is studied in the research clinic. Sodium lactate infusion is said to reliably provoke panic in patients with panic disorder (10), but at least one-third of patients and possibly more have no marked response (11). Hyperventilation is an important part of the pathogenesis of panic, but probably at least 50% of patients with panic disorder show no evidence of chronic hyperventilation when evaluated at rest (12). Desensitization and exposure may be the best remedy for phobic avoidance, but substantial numbers of patients do not respond to these treatments or to other forms of psychotherapy, including dynamic psychotherapy.

Indeed, even the three divisions of the illness elucidated by Klein cannot possibly deal with all the subtle clinical variations. For example, the degree to which panic attacks are actually "spontaneous" has been debated. At least three studies (13–15) have reported that panic attacks frequently begin in the context of adverse life events. If a patient has recently suffered a substantial personal loss and then has the first panic attack, does this mean the attack has a psychosocial trigger and therefore is not spontaneous? How do we classify the patient whose anticipatory anxiety level is so great that individual panic attacks are no longer distinguishable from the background of chronic anxiety? And where in this system should we fit clinical depression, which appears to strike victims of panic disorder at a higher rate than nonanxious control subjects?

Despite these difficulties, Klein's phenomenology of

panic lends itself well to an overall neuroanatomical classification. As will be discussed, a certain amount of variance from this tripartite system can be assumed without substantial violence to the theory.

PANIC ATTACKS AND THE BRAINSTEM

Two lines of evidence indicate that acute panic attacks are generated by neural discharge in the brainstem. The first is the clinical observation that panic attacks are largely experienced by patients as storms of autonomic nervous system activity. The second is the extensive laboratory work in which panic attacks are provoked by pharmacological agents.

One of the most striking features of a patient's description of an acute panic attack is the physical nature of the symptoms. Unlike other forms of anxiety, in which affects like worry and tension predominate, patients with panic disorder invariably begin describing the illness with reference to their hearts, lungs, gastrointestinal tracts, and "nerves." In two studies (16, 17), the amount of purely physical complaint in panic disorder distinguished it from the more "emotional" complaints of patients with generalized anxiety disorder.

It is the physical symptoms of panic disorder that are most reliably reproduced by the various laboratory provocations of panic. Investigators have now shown conclusively that the patient with panic disorder can be made to have an anxiety attack in the laboratory if given one of a number of pharmacological agents. The best studied to date are sodium lactate (18), carbon dioxide (19–21), yohimbine (22, 23), caffeine (24, 25), isoproterenol (26), and norepinephrine (27).

Not all laboratory stressors induce panic. Cognitive stress, such as the mental arithmetic test (28; unpublished 1986 study by Margraf et al.), does not seem to provoke panic attacks, although it can make the subject anxious. Similarly, pain (29) and hypoglycemia induced by the glucose tolerance test (30) or insulin (31) do not cause panic attacks. Panic attacks have even been described in the laboratory as a consequence of relaxation training when the subject least expects to experience anxiety (32). Anxious cognition or physiological discomfort alone, then, appear to be neither sufficient nor necessary to trigger panic in the early stages of the illness.

In the laboratory, the patient undergoing a lactate infusion, yohimbine ingestion, or carbon dioxide inhalation usually complains first of palpitations, difficulty catching his or her breath, dizziness, lightheadedness, paresthesias, and sweating. Some normal control subjects may complain of these as well, but only the patient quickly develops overwhelming dread and fear that disastrous physical consequences are imminent. Typically, the patient insists that the offending substance be "turned off" and the procedure is terminated.

This sequence of events nicely parallels what occurs during at least the first flurry of panic attacks in the

career of someone about to develop panic disorder. That is, the patient seems to experience a sudden crescendo of autonomic nervous system symptoms and then fears that death must be at hand. Studies have now indicated, for example, that the kind of panic attack experienced during a lactate infusion is a close replica of the kind spontaneously experienced *in vivo* by patients with panic disorder (33).

Consequently, it is important to ask what neurological effects the various panicogenic agents have that induce panic in susceptible individuals. It is not easy to answer this question because the various agents have diverse effects and controversies exist between competing laboratories. In the case of isoproterenol, a somewhat weaker panicogen than lactate (34), it is difficult to speculate on its CNS effects because, as far as is known, it does not cross the blood-brain barrier.

The three agents that have been most extensively studied are sodium lactate, carbon dioxide, and yohimbine hydrochloride. It is most likely that each one of these has its primary effect on one or more brainstem loci that, when triggered, provoke the massive autonomic discharge characterizing the panic attack.

Yohimbine has perhaps the best understood CNS effect of the many panicogens. It is well-known that this α_2 -adrenergic receptor antagonist provokes increases in CNS noradrenergic discharge and raises the firing rate of the pontine nucleus, the locus ceruleus. The locus ceruleus is the center of noradrenergic activity in the CNS. A metabolite of noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG), is reliably increased by yohimbine administration (35) and therefore serves as a peripheral marker of its central effects.

Clinically, the first observation that yohimbine may be anxiogenic came from intravenous experiments performed on a variety of psychiatric inpatients by Garfield et al. (36) and Holmberg and Gershon (37). They specifically observed that higher levels of baseline anxiety seemed associated with a greater anxiogenic response to yohimbine.

Preclinically, the important experiments of Redmond (38, 39) in the stump-tailed monkey demonstrated that electrical stimulation of the locus ceruleus produced a panic-like response. Ablation of the locus ceruleus, on the other hand, rendered monkeys less vulnerable to anxiety-provoking stimuli.

This finding lead Charney et al. (22) to administer yohimbine to patients with panic disorder in oral doses of 20 mg. Patients developed greater anxiety and more frequent panic attacks than normal control subjects. MHPG levels increased in the subjects, confirming that yohimbine was indeed increasing central noradrenergic turnover.

From this work, it has been hypothesized that panic attacks are triggered by increased firing of the brainstem noradrenergic center, the locus ceruleus. According to this hypothesis, drugs that reduce the locus ceruleus firing rate should prevent panic attacks.

The most directly acting such drug is clonidine, an α_2 -adrenergic agonist that, through a negative feed-

back loop, lowers the locus ceruleus firing rate. Two studies (40, 41) have shown that clonidine does have transient antipanic effects, but side effects make it an undesirable clinical choice.

Acute clonidine administration also produced a greater decrease in the anxiety and plasma MHPG levels of patients with panic disorder than in those of normal control subjects (42, 43). This was interpreted as further indication of noradrenergic dysregulation in patients with panic disorder. Other work has shown that acute clonidine administration is anxiolytic (44, 45) and blocks anxiety associated with withdrawal states (46, 47).

Chronic administration of the drugs most often associated with clinical utility in the blockade of panic—imipramine and desipramine—also reduce central noradrenergic turnover and the locus ceruleus firing rate (48, 49).

The noradrenergic theory is not without important problems and controversy. First, Garfield et al. (36) and Holmberg and Gershon (37) did not specifically study patients with panic disorder; therefore, the specificity of their finding is in doubt. Second, both Mason and Fibiger (50) and Koob et al. (51) from Bloom's laboratory have criticized the original work by Redmond (38, 39), insisting that the locus ceruleus mediates arousal, not anxiety, in animals.

The work of Charney et al. (22) has been questioned because only patients with at least two panic attacks per week, rather than the broader class of patients with panic disorder in general, had significantly greater MHPG increases than control subjects during yohimbine administration. Also, Uhde (52) replicated the Charney finding on one occasion, but Uhde et al. (unpublished 1986 paper) were unable to do so on another. Uhde et al. attributed the discrepancy to higher baseline anxiety in patients in the first study who did experience panic from yohimbine than in the patients in the second study who did not panic.

Although imipramine, which blocks spontaneous panic, may indeed reduce the locus ceruleus firing rate, it has been found to have no effect on yohimbine-induced anxiety (53) or to make it worse (36). Buspirone, a newly introduced nonbenzodiazepine anxiolytic, actually stimulates locus ceruleus discharge (54) but has yet to be reported to provoke panic. It may increase anxiety when given in very high doses (55).

Also, MHPG increases were not seen in panic attacks provoked by lactate infusion (56), carbon dioxide inhalation (57), or naturalistic exposure to phobic stimuli (57). Finally, Kaitin et al. (57) found that electrical stimulation of the human locus ceruleus did not produce a panic reaction.

Despite these reservations, yohimbine seems clearly capable of provoking panic in at least some patients with panic disorder and its action is very likely mediated through a brainstem locus.

This is also the case with carbon dioxide inhalation, which has now been shown to provoke panic in pa-

tients with panic disorder, but not in normal control subjects, in a number of laboratories (58). Although the neural effects of carbon dioxide are well understood, they are complex and their applicability to an understanding of panic disorder consequently requires careful explication.

Room air normally contains almost no carbon dioxide. Increasing the amount of carbon dioxide in inspired air has an automatic effect of increasing minute ventilation (i.e., the product of respiratory rate and tidal volume). This is mediated through several classes of receptors, located respectively in the lungs, the aortic arch and carotid bodies, and the surface of the medulla (59). In addition, Elam et al. (60) have shown that carbon dioxide inhalation in animals causes a dose-dependent increase in firing rate of the locus ceruleus.

Among those patients who had panic attacks during 5% carbon dioxide inhalation in our laboratory, we observed a significantly more rapid increase in minute ventilation before the panic than in nonpanicking patients or normal control subjects (20). In other words, not only did these patients have panic attacks, they also exhibited a hyperactive ventilatory response to carbon dioxide. This indicates greater carbon dioxide sensitivity in the patients. Using higher concentrations of inhaled carbon dioxide and a different method of carbon dioxide administration (i.e., the Read rebreathing method), Woods et al. (21) did not find such evidence of carbon dioxide hypersensitivity in patients with panic disorder. Hence, methodological differences probably explain the discrepant findings.

In our laboratory, furthermore, we applied a measure called inspiratory drive to the same subjects who had panic attacks during carbon dioxide administration and found that it, in parallel to minute ventilation, also increased more quickly in the panicking patients than nonpanicking patients or control subjects (20). Because respiratory physiologists believe that inspiratory drive assesses the brainstem or medullary component of control over respiration (61), we tentatively concluded that panicking patients have more sensitive brainstem carbon dioxide receptors than normal control subjects.

Sodium lactate infusion is the most extensively studied laboratory method of provoking panic. Sodium lactate-induced panic has been shown to be specific to patients with a history of spontaneous panic attacks (62–66), to provoke panic that closely resembles naturally occurring panic (64), and to be blocked by all agents known to block clinical attacks (i.e., tricyclics, monoamine oxidase inhibitors [MAOIs], and alprazolam) (28, 67, 68).

Study of lactate-induced panic has shown what biological events occur during panic attacks, including hyperventilation, tachycardia, increased blood pressure, and increased plasma noradrenaline level (69). Understanding why lactate causes panic, however, has been exceedingly difficult. Lactate infusion produces a number of peripheral physiological and biochemical

effects but no well-characterized CNS effect. We observed a paradox in the physiological response to infused lactate, however, that pointed the way to a possible explanation of lactate panic.

Infused lactate is metabolized to bicarbonate on a mole for mole basis (70). Consequently, lactate infusion induces a metabolic alkalosis. Normally, the pulmonary response to metabolic alkalosis is hypoventilation, which acts to retain carbon dioxide and thereby to return pH to normal (71). We have observed, however, that patients who panic during lactate infusion actually hyperventilate (12, 72).

This paradox may be explained by the fact that bicarbonate, which does not readily cross the blood-brain barrier (73), is further metabolized to carbon dioxide, which quickly permeates the CNS. Hence, there may be a buildup centrally of carbon dioxide, which, as described earlier, would immediately increase ventilatory rate. Sodium lactate infusion, therefore, may well act like carbon dioxide inhalation and stimulate the central medullary chemoreceptor. Thus, laboratory work with sodium lactate, yohimbine, and carbon dioxide all implicate irritable foci in the brainstem—especially the pons (locus ceruleus) and medulla (chemoreceptors)—as the source of panic.

The locus ceruleus and medullary chemoreceptors may be further linked to each other. Work with rats indicates that the primary stimulatory afferent projection to the locus ceruleus comes from the medullary nucleus paragigantocellularis (74). Maximal inspiration in cats is produced by stimulation of the adjacent medullary nucleus gigantocellularis (75). Stimulation of medullary chemoreceptors by carbon dioxide will cause increased firing of the nucleus reticularis gigantocellularis, which in turn provokes the locus ceruleus. Hyperventilation will also result during stimulation of these nuclei.

Even substances that are said to provoke panic but do not cross the blood-brain barrier—like isoproterenol and norepinephrine—may indirectly stimulate the medulla. These substances produce blood pressure alterations that trigger the peripheral baroreceptors. Impulses from the baroreceptors travel through the vagus nerve to the medullary brainstem nucleus solitarius (76). Ascending tracts, such as the tract of the nucleus solitarius, further innervate the nucleus reticularis gigantocellularis and then the locus ceruleus.

Another area of the brainstem needs to be considered—the serotonergic neurons of the dorsal raphe region of the midbrain. Several lines of evidence indicate that serotonergic transmission may also play an important role in the genesis of a panic attack. Preclinically, stimulation of the raphe area in animals causes anxiety-like responses (77).

Sodium lactate has been shown *in vitro* to increase platelet uptake of serotonin (78) and *in vivo* to cause increase in serum prolactin level (56). The latter is considered evidence of central serotonergic stimulation (79), although other neurotransmitter systems are involved as well.

In patients with panic disorder, several medications with main activity on serotonin transmission have been found to block panic attacks. These include zimelidine (80), clomipramine (81), L-5-hydroxytryptophan (82), and fluoxetine (83).

Studies specifically stimulating serotonergic function in patients with panic disorder have now been reported by a few laboratories and yield discrepant data. Charney and Heninger (84) found that tryptophan infusions did not produce differential increases in serum prolactin levels in patients than in control subjects, evidence against serotonergic dysfunction in panic. Charney et al. (85) also administered 0.1 mg/kg of the serotonergic agonist meth-chlorophenylpiperazine (MCP) intravenously to patients with panic disorder and control subjects and found both groups reacted with equal increase in anxiety. Although this would argue against a specific serotonergic mechanism for panic, Kahn et al. reported in an unpublished 1987 paper that giving smaller doses of MCP than used in the negative study (0.25 mg/kg orally) produced panic attacks in 50% of patients with panic disorder but not in any normal control subjects. Thus, patients with panic disorder may have a lower threshold to MCP response than normal control subjects because of hypersensitive serotonergic receptors.

A number of animal studies have indicated that the locus ceruleus is under substantial influence of serotonergic nuclei in the pontine and midbrain raphe areas (86). Fibers of the median raphe nucleus project caudally to the locus (87).

It is interesting that these serotonergic neurons generally also contain cotransmitters, believed to act as modulators of neural transmission, such as substance P, enkephalins, and TRH (88). Little work has been done on the role of these transmitters in panic disorder.

The accumulated laboratory evidence, gleaned mainly from provocation studies, accords best with the idea that panic attacks begin with stimulation of irritable foci in one of three brainstem areas—the medullary chemoreceptors, the noradrenergic pontine locus ceruleus, or the serotonergic midbrain dorsal raphe. Some combination of the three may also be involved, since both medullary and midbrain raphe nuclei directly innervate the locus ceruleus.

Of course, patients with panic disorder are not intermittently bombarded with sodium lactate, increased carbon dioxide levels, or yohimbine. Hence, we must assume that these patients inherit brainstem loci that are hyperexcitable and that some process, either endogenous toxin or aberrant neural transmission, excites them. The work of Torgersen (89) and Kendler et al. (90) seems more than adequate to assure that panic disorder is substantially a genetic disease.

Several interesting research and clinical observations can be explained with reference to a brainstem locus for acute panic. It is possible, for example, that the putative brainstem locus or loci are prone to peripheral excitation as well. Perhaps one function of the hypothesized brainstem locus for panic is to monitor the re-

relationship between peripheral physiological function and metabolic demands. Information about heart rate and rhythm and about ventilatory function is conveyed through vagal afferents to the nucleus solitarius of the medulla (91). Afferents then traverse the tract of the nucleus solitarius to other parts of the brainstem (92). Any mismatch between peripheral autonomic activity and actual metabolic demand, as in the case of isoproterenol infusion or sudden fright, may be capable of stimulating a hypersensitive locus in the brainstem and initiating the cascade of neural events necessary for panic.

In line with this, we and others have found that exercise stress tests do not cause panic attacks in patients with panic disorder even though they develop very rapid heart and ventilatory rates (93 and our unpublished data). However, in the case of exercise, increases in heart and ventilatory rate are in synchrony with metabolic demand and consequently would not stimulate the brainstem according to the present hypothesis.

Levinson (94) claimed that patients with panic disorder suffer from disturbances of vestibular function, which can be corrected by administration of antihistamines. Scientific support for this notion comes from one uncontrolled study (95) in which a variety of otoneurological abnormalities were found in a group of patients with panic disorder.

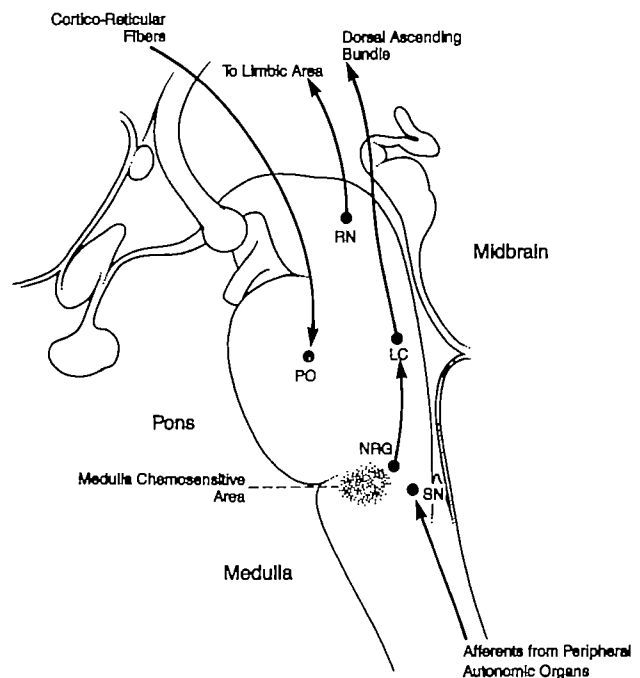
The present model offers an alternative and perhaps more parsimonious explanation for the common complaints of dizziness and unsteadiness during acute panic. Pontine nuclei, including the locus ceruleus, project to the cerebellum (96). Discharge from the brainstem, therefore, may stimulate cerebellar centers that control vestibular function and thereby provoke symptoms similar to vertigo.

Finally, in addition to autonomous discharge and peripheral innervation, the putative brainstem loci for panic described here can readily be stimulated by descending pathways originating in higher cortical areas of the CNS. This method of provoking panic, discussed in more detail later in this paper, explains the mechanism behind the induction of panic by adverse life experiences.

Figure 1 indicates the pathway by which an acute panic attack begins according to the present hypothesis. The locus ceruleus may be central because its stimulation produces almost all of the physiological and autonomic signs of panic. The locus ceruleus, on the other hand, is directly innervated by fibers originating in the periphery that project through the vagus nerve to the medullary nucleus solitarius; by fibers from chemosensitive nuclei in the medullary reticulum, including the nucleus reticularis paragigantocellularis; and by descending serotonergic fibers from midbrain raphe nuclei.

Reference to a brainstem origin of panic explains the sudden, unpredictable onset of the attack and the predominance of autonomic symptoms during the attack. It further accounts for data collected from laboratory

FIGURE 1. Hypothesized Pathway by Which an Acute Panic Attack Begins: Origin in the Brainstem*



*RN=raphe nuclei; PO=pontis oralis; LC=locus ceruleus; NRG=nucleus reticularis gigantocellularis; SN=solitary nucleus.

provocation of attacks and for genetic data indicating that this condition is highly heritable. Finally, such a view may explain why any stimulus, including sudden fright, that creates an asynchrony between metabolic demand and physiological function may be capable of causing a panic attack in a susceptible individual.

THE LIMBIC LOBE AND ANTICIPATORY ANXIETY

There is ample reason to speculate on both experimental and theoretical grounds that anticipatory anxiety is a limbic lobe phenomenon.

The limbic lobe is believed to be the center of many basic human emotions, including rage, arousal, and fear. In experimental animals, irritative lesions of limbic structures produce fear and terror responses (97). Penfield (98) made similar observations with human subjects. Lesions of the cingulate portion of the limbic lobe, which contains fibers running from the brainstem to the frontal cortex and from the frontal cortex to the parahippocampal gyrus, lead to decreases in anxiety in man (99).

Anticipatory anxiety seems a characteristic form of basic human emotion: patients usually have difficulty explaining precisely what it is they dread once they have had a number of panic attacks. They have a vague sense that future attacks may occur and that this will be disastrous. This form of anxiety generally strikes the clinician as preverbal, too complex for brainstem origin but not complex enough for origin in a higher

cortical center. It is often only the clinician who can translate this nearly inchoate emotion into the specific fear of having further attacks. Characteristically, once this is explained the patient almost automatically nods in agreement as if a basic chord has been struck.

Gray et al. (100, 101) have long argued that generalized anxiety is produced by locus ceruleus influence over the hippocampal area of the limbic system. More specifically, they suggested that locus ceruleus inhibition of hippocampal activity provokes generalized forms of anxiety. Gray et al. marshaled substantial animal research in favor of this idea.

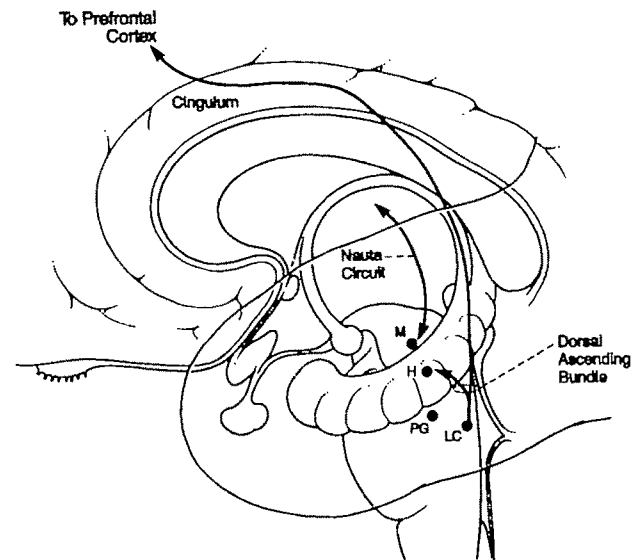
It is of note in this regard that although benzodiazepines such as diazepam have little effect on acute panic attacks in doses normally prescribed, they are quite effective in blunting anticipatory anxiety (102). Furthermore, our group (64) showed that intravenous diazepam produced marked reduction in generalized anxiety in patients with panic disorder but did not block the ability of sodium lactate to cause actual panic. The limbic area of the human brain is particularly rich in benzodiazepine receptors (103). Thus, our proposed neuroanatomical hypothesis can be used to explain why benzodiazepine medication is effective in treating one specific portion of the disease—anticipatory anxiety—but not another—the panic attack.

Evidence that anticipatory anxiety may be of limbic origin also comes from the important work of Reiman et al. (104, 105). In their studies, patients with panic disorder and normal control subjects underwent brain imaging with the positron emission tomography (PET) method. PET scanning was performed minutes before the subjects underwent sodium lactate infusion.

Only those patients who went on to panic during the subsequent infusion showed an abnormal symmetry in blood flow through a specific limbic structure, the parahippocampal gyrus. Because the abnormality was found in subjects about to have an attack, it probably represents the cortical events of anticipatory anxiety, although this needs confirmation by further study. It would be of great interest to learn whether reduction in anticipatory anxiety, either through benzodiazepine administration or relaxation techniques, restores blood flow through the parahippocampal gyrus to normal levels without affecting the subsequent tendency to have an actual panic attack during lactate infusion. This would be dramatic evidence of an anatomical difference between panic and anticipatory anxiety.

According to our hypothesis, activation of one or more brainstem loci during acute panic further innervates limbic lobe structures to produce anticipatory anxiety. Figure 2 details the relevant pathways. In this regard, there are well-defined neural pathways linking both the locus ceruleus (through the dorsal ascending bundle [106]) and the midbrain (through the so-called Nauta circuit [107]) to the limbic lobe. According to Papez (108), the limbic lobe in turn modulates cortical influences over the brainstem reticular activating system. There are ascending pathways, for example, from the brainstem to the amygdala to the frontal cortex

FIGURE 2. Hypothesized Pathway by Which Anticipatory Anxiety Occurs: Site in the Limbic System*



*M=midbrain; H=hippocampus; PG=parahippocampal gyrus; LC=locus ceruleus.

and reciprocal descending pathways through the same structures (109).

The ability of panic attacks to produce generalized anxiety may be viewed as an example of the kindling phenomenon. According to this view, repeated stimulation of limbic neurons by brainstem discharge lowers the threshold to excitatory postsynaptic stimulation in the limbic lobe until "subpanic" stimulation is capable of maintaining the "kindled" anticipatory anxiety. Thus, even without the further occurrence of panic, the limbic area continues to have a reduced threshold for response to various stressors. Post and Uhde (110, 111) have extensively detailed the relevance of kindling phenomena to psychiatric disorders, including panic.

The limbic area of the brain is peculiarly prone to kindling phenomena (112). Brainstem stimulation has been shown to produce kindling in limbic structures in the rabbit (113). There may be a genetic relationship between fearfulness and a propensity for kindling in the feline limbic area (114). Repeated electroshock both kindles limbic nuclei and leads to an increase in benzodiazepine receptor density in the hippocampus (115). Benzodiazepines, in turn, are effective in blocking kindled responses (116).

Thus, benzodiazepines block both kindling and anticipatory anxiety, and brainstem stimulation of the limbic lobe may produce both phenomena. Kindling of the limbic lobe by brainstem stimulation during panic attacks may indeed be the etiology of anticipatory anxiety.

In addition to receiving direct neural stimulation from the brainstem during panic attacks, areas of the limbic lobe may be particularly sensitive to the changes in cerebral blood flow caused by acute hyperventila-

tion. As mentioned earlier, work in our laboratory and others has shown that hyperventilation is an integral part of the panic attack. Hyperventilation-induced hypocapnia is a potent stimulus for cerebral vasoconstriction, thus producing a dramatic decrease in cerebral blood flow and relative tissue hypoxia. Many believe that the dizziness, disorientation, and derealization that often accompany panic are secondary to hyperventilation and reduced cerebral blood flow. Possibly, these effects further sensitize the limbic area.

Clinically, anticipatory anxiety can become a greater problem for the patient than panic attacks themselves. In many cases, even when the attacks spontaneously cease to occur, the patient still dreads having them. Such patients may experience high levels of anticipatory anxiety merely by thinking of a situation associated with having an attack, such as driving a car or going into a restaurant. At times, it appears that the level of anticipatory anxiety reaches a point that by itself triggers an actual attack. This may explain the finding that patients who panic during sodium lactate infusion had higher baseline levels of anxiety immediately before infusion than nonpanicking patients (11).

In these cases, limbic lobe activation may stimulate the brainstem through descending pathways and ultimately trigger panic. Antipanic medication may raise the threshold of brainstem firing to too high a level for limbic lobe discharge to have this effect; this would explain the often encountered clinical phenomenon in which patients taking antipanic medications state that they felt "as if" an attack were about to come on but no attack actually developed despite high levels of anticipatory anxiety.

On the other hand, any measure that decreases anticipatory anxiety by quieting the limbic lobe removes one more trigger to panic and makes the actual panic attack less likely to occur. Here, behavioral techniques such as breathing retraining and relaxation may be especially important. Although most clinicians, psychopharmacologists and behaviorists alike, do not report that such measures alone actually block attacks, they seem to work in much the same way as standard benzodiazepines by rendering the patient much less likely to have an attack. Furthermore, patients who regularly practice breathing and relaxation exercises or who take benzodiazepines without taking antipanic medication often state that they are able to cope with or "ride through" the attack more easily.

An alternative view to that presented thus far is that limbic lobe discharge is central to the development of the panic attack itself. This view could be supported on two grounds. First, there is evidence (117, 118) that direct electrical stimulation of human limbic structures produces panic-like sensations. In line with this are two studies (36, 119) linking epileptic-like symptoms to panic attacks. Second, there is some evidence that benzodiazepines are more effective antipanic agents than previously thought. Alprazolam, a triazolobenzodiazepine, is clearly an effective antipanic drug. It is not known whether alprazolam has this property be-

cause of its greater potency than other benzodiazepines or because of pharmacological properties that appear to distinguish it from the traditional benzodiazepines (120–122). Support for the higher potency idea comes from a recent report that the high-potency benzodiazepine clonazepam has antipanic activity (123). Pending further preclinical and clinical investigation, it remains unknown to what extent and by what mechanism benzodiazepines specifically treat panic attacks in addition to anticipatory anxiety. Our hypothesis asserts that panic is of brainstem origin, but the possibility also exists that limbic discharge could itself initiate panic.

According to the model proposed so far, then, the fact that various treatments appear to affect different features of the illness can be explained by a difference in neuroanatomical locus. Although only interventions that directly desensitize the irritable brainstem foci for panic can actually block attacks, interventions that desensitize higher neural loci in the limbic lobe may actually produce greater clinical benefit, especially in patients for whom anticipatory anxiety, rather than panic, has become the dominant feature of the illness.

THE PREFRONTAL CORTEX AND PHOBIC AVOIDANCE

It is not difficult to conceive of even relatively primitive forms of animals experiencing panic attacks and anticipatory anxiety. Even goldfish respond to anxiolytics (124). Indeed, many of the experiments discussed thus far involve animal models of anxiety that extend far down the phylogenetic tree.

Phobic avoidance is, of course, not limited to higher mammals. After repeated presentation of an aversive stimulation, most animals will learn to avoid either the aversive stimulus, situations associated with the stimulus, or both (125, 126). However, after prolonged absence of the aversive stimulus, such avoidance usually extinguishes in lower animals. For example, extensive study of the marine snail *Aplysia* reveals it can be sensitized to a noxious stimulus. Kandel and Schwartz (127) noted, however, that the learned behavior must be continually reinforced or it extinguishes: "A single noxious sensitizing stimulus produces a memory that lasts several hours. With four consecutive noxious stimuli, the memory lasts one day. Sixteen consecutive stimuli prolong the memory to several days, and with 16 spaced stimuli (four per day for four days) it lasts several weeks" (p. 439). Apparently, the more complex the organism the longer it can remember to avoid noxious stimuli without continual reinforcement.

Humans thus have the distinction of maintaining phobic avoidance long after the aversive stimulus has ceased to be applied. In a few cases, the aversive stimulus is applied only once but phobic avoidance develops and persists. Thus, it is not unusual to encounter agoraphobic patients who have actually had only one or two panic attacks yet remain avoidant for several

years of situations in which those few attacks originally occurred.

Phobic avoidance is a truly learned phenomena that involves substantial conscious cognitive capacity. Although relatively primitive areas of the neuroaxis are here postulated to be the centers for panic and anticipatory anxiety, a higher cortical center must be the locus of phobic avoidance.

Clinically, blockade of panic attacks with antipanic medication often does not relieve phobic avoidance. Psychotherapeutic approaches aimed at teaching the patient that nothing serious will actually occur during exposure to phobic stimuli is then required. Such treatments are varied, ranging from simple explanation of this fact to the patient and cajoling him or her into the phobic situation to more formal combinations of hierarchical in vivo desensitization and cognitive restructuring.

Discharge from the brainstem during the actual panic attack, then, is probably ultimately interpreted by centers in the prefrontal cortex, the area of the higher brain most involved with learning and complex emotion. Here, the attack is labeled as a dangerous, life-threatening event. Also, it is in the prefrontal cortex that associations are made between the autonomic storm of the attack itself and the environmental situations and cognitions that happened to accompany the attack.

Thus, the patient makes the judgment that the situation he or she was in at the time of the attack—driving a car over a bridge for example—has provoked the attack. Similarly, the patient decides that whatever conscious thoughts were occurring at the time of the attack—perhaps an angry thought about a spouse or a fear of separation from a romantic involvement—have etiological significance in the generation of the attack.

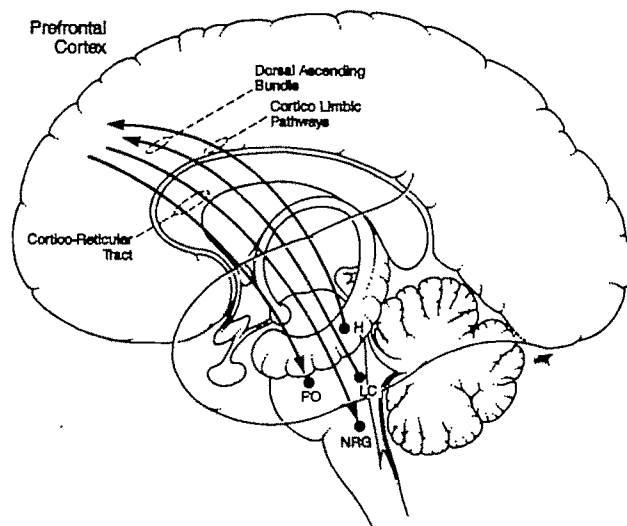
Consequently, the patients learn to fear driving over a bridge, having angry thoughts or confrontations with a spouse, or separating from someone with whom they are romantically involved. Such situations and cognitions are judged to be dangerous because they may provoke a “life-threatening” panic attack.

Not only are these beliefs strengthened by anticipatory anxiety, representing discharge from the limbic lobe, they reciprocally act through descending pathways to further stimulate the limbic areas and maintain anticipatory anxiety. There are extensive anatomical connections between the prefrontal cortex and limbic structures (128). For this reason, behaviorists have learned to combine relaxation techniques with desensitization therapy in order to reduce anticipatory anxiety during exposure to phobic stimuli.

These pathways between the prefrontal cortex and the limbic lobe can also explain the basis of reported cases of agoraphobia without panic attacks. Phobic avoidance and anticipatory anxiety could conceivably be maintained without the induction of panic if only these reciprocal pathways between prefrontal cortex and limbic areas were involved.

Finally, afferent pathways from the frontal cortex to

FIGURE 3. Hypothesized Pathway by Which Phobic Avoidance Occurs: Development in the Prefrontal Cortex*



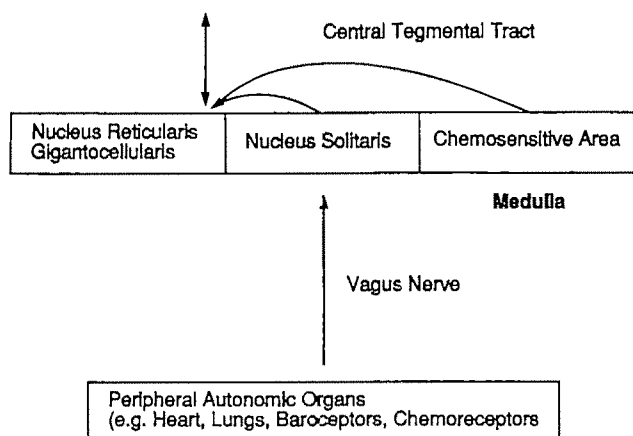
*H=hippocampus; PO=pontis oralis; LC=locus ceruleus; NRG=nucleus reticularis gigantocellularis.

the brainstem enable learned associations and catastrophizing cognitions originating in the prefrontal cortex to stimulate brainstem loci and cause panic attacks. Specifically, as shown in figure 3, the corticoreticular pathway that terminates on the nuclei pontis oralis in the pons and on the nucleus reticularis gigantocellularis of the medulla (129) may be the mechanism for cognitively generated panic. It must be remembered that the latter nucleus is adjacent to the medullary nucleus paragigantocellularis, the source of the major stimulatory innervation of the locus ceruleus (74). Thus, a loop exists from the medullary reticular area to the locus ceruleus and, through the dorsal ascending bundle, to the limbic lobe and prefrontal cortex and then back to the reticular nuclei of the brainstem, especially the nucleus reticularis gigantocellularis. These neural pathways, shown schematically in figures 4 and 5, constitute the “panic disorder circuit.” Once again, reference to the neuroanatomical model helps explain a number of common clinical situations.

Some agoraphobic patients state emphatically that only exposure to feared situations results in panic. Such patients rarely report having attacks while staying at home. In such patients it is probable that the original stimulant to spontaneous panic is quiescent and only prefrontal cortical stimulation of the brainstem can result in attacks.

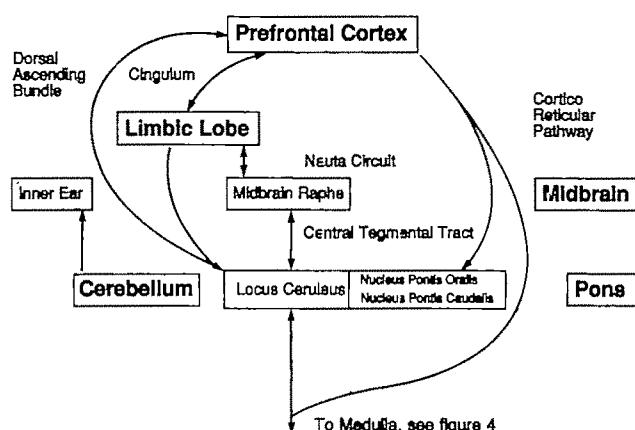
There are patients, on the other hand, who are successfully desensitized from their phobias but still have attacks. Such patients often use a variety of cognitive and behavioral techniques to weather the attack and manifest little phobic avoidance. In these patients, prefrontal cortical stimulation is controlled. Nevertheless, spontaneous attacks erupting from autonomous

FIGURE 4. Schematic Diagram of the Pathways Hypothesized To Be Involved in Panic Disorder^a



^aContinued in figure 5.

FIGURE 5. Schematic Diagram of the Pathways Hypothesized To Be Involved in Panic Disorder



stimulation of the brainstem have not been cured. Placing such patients on antipanic medication often results in blockade of the attack while remission from phobic avoidance remains intact.

EXPERIMENTAL TESTS OF THE HYPOTHESIS

Because of its complexity, a great many experiments will be required to either validate or disprove our model. Although an explication of all the experimental steps required would necessitate another paper, we would specifically predict the following if our hypothesis is correct.

1. Animal experiments, such as those showing that locus coeruleus stimulation in monkeys causes anxiety, should show that stimulation of medullary chemoreceptors and the nucleus reticularis gigantocellularis produces identical panic-like responses.

2. Administration of carbon dioxide, yohimbine, sodium lactate, and isoproterenol should cause anxious

responses in animals similar to those caused by electrical stimulation of the hypothesized medullary and pontine panic center.

3. In patients with panic disorder, administration of benzodiazepines or use of simple relaxation techniques should not block the panicogenic effect of carbon dioxide, lactate, yohimbine, or isoproterenol.

4. When they become available, imaging studies done during laboratory provocation of anxiety should show acute changes in brainstem activity. Knott and Lapierre (130), by examining brainstem auditory evoked potentials, showed that the brainstem is activated in patients with panic disorder during lactate-induced panic.

5. Benzodiazepine administration should correct the abnormal parahippocampal gyrus blood flow seen during PET scan studies of patients with panic disorder because this is hypothesized to be a manifestation of limbic-lobe-driven anticipatory anxiety. Tricyclic antidepressants and MAOIs, which do not affect anticipatory anxiety directly, should not influence this blood flow pattern.

6. Clinical studies should further substantiate the claim that benzodiazepines block anticipatory anxiety but not panic. At present this prediction does not include the triazolobenzodiazepine alprazolam, whose mechanism of action in panic disorder is unclear but may involve properties distinct from traditional benzodiazepines. If data accumulate that benzodiazepines are indeed antipanic, the present hypothesis would be amended to include the possibility that limbic discharge is itself directly panicogenic.

7. Exposure to phobic stimuli—either in the form of pictures, videotapes, or imagination—of phobic patients during brain imaging studies should produce specific activation in the prefrontal cortex.

8. Clinical studies should substantiate the claim that agoraphobic patients who are successfully treated with cognitive-behavioral treatment will still suffer from occasional panic attacks despite the loss of phobic avoidance. This does not imply that behavioral-cognitive treatments are ineffective—they clearly benefit patients—but, rather, that they exert ameliorative effects at a different “site” of disease progression than do antipanic drugs.

9. Cognitive-behavioral treatments should lead directly to a decrease in prefrontal cortical activity during brain imaging studies when the patient is exposed to a phobic stimulus. Drug treatment alone should not be successful in this regard.

CONCLUSIONS

According to our model, different treatments for panic disorder and agoraphobia not only affect different parts of the illness but also different parts of the CNS. Thus, antipanic drugs (imipramine, phenelzine, and alprazolam) block brainstem-provoked panic attacks; relaxation and breathing training and benzodi-

azepines reduce anticipatory anxiety; and desensitization and cognitive therapies relieve phobic avoidance.

So far, no specific mention has been made of dynamic psychotherapies. Nemiah (131) reviewed the psychoanalytic theory for the generation of anxiety symptoms. Cooper's comments on the overlap between the biological and psychodynamic approaches to psychiatric illness (132) are also relevant.

Essentially, the model proposed here neither contradicts nor validates psychoanalytic theory or the utility of psychodynamic treatment for panic disorder. One might hypothesize that the basic underlying proclivity to have an attack, which has been ascribed here to genetic traits, is actually at least partially secondary to unconscious conflict. Alternatively, just as we have speculated that discharge from the frontal cortex developing from learned associations and catastrophizing cognitions can stimulate the brainstem to cause panic, it may well be that "signal anxiety" generated by unconscious conflict, as originally defined by Freud (133), can also initiate the cascade of events that ultimately leads to panic. Controlled trials of psychodynamic psychotherapy in the treatment of the different facets of anxiety disorder would clearly be immensely useful in this regard.

Panic disorder is one of the most prevalent and well-studied psychiatric disorders. Consequently, it has become the focus of controversy that has generalized to encompass many of the fundamental issues in modern psychiatry. Our hypothesis is ambitious in its attempt to account for all aspects of the illness. Undoubtedly, some of its aspects will not withstand rigorous clinical or neuroanatomical research. Nevertheless, there are several principles inherent in this model that require emphasis.

First, it regards the neural circuits of the brain as the basis for pathology. Almost every clinical feature of this very heterogeneous condition is accounted for by specific neural pathways.

Second, the theory attempts to account for the success of different types of treatment, both pharmacological and nonpharmacological. Although it is a biological hypothesis in the sense that it involves real neuroanatomical pathways, the hypothesis is sensitive to psychological interventions in a variety of ways.

In the future, if this model is adopted, it will no longer be necessary in order to assert that a specific medication works in the treatment of panic to also assert that medications of other classes or various psychotherapies do not also work. Rather, each treatment has an important effect on a specific part of the illness and for specific patients manifesting the various aspects of the syndrome.

Finally, the theory accounts for the many seemingly contradictory ideas of what causes panic disorder. The admirable work of groups studying central noradrenergic function, caffeine response, behavioral treatment, genetics, and cognitive disturbance in patients with panic disorder is combined rather than opposed.

The hypothesis is complex, but a complex disorder

involving so many aspects of neurobiology, autonomic nervous system function, behavioral disturbance, and psychological impact requires a complex theory of etiology. We hope that such an attempt will serve to foster collaborative work in multidisciplinary areas.

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How Are Depression and Bulimia Related?

Alan B. Levy, M.D., Katharine N. Dixon, M.D., and Stephen L. Stern, M.D.

The idea that bulimia may be related to affective illness was encouraged by early reports of a high prevalence of clinical depression in bulimic patients as well as a high lifetime prevalence of depression in the families of these patients. More recent evidence suggests, however, that bulimia and major depression are distinct entities. The authors review clinical data, family studies, pharmacotherapy, and the neurobiology of bulimia and discuss the nature of the relationship between depression and bulimia.

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Earlier in this decade reports began to accumulate that suggested a possible relationship between bulimia and depression. Clinical symptoms of depression (1-11) and high rates of familial depression (8, 12, 13) were frequently described in samples of bulimic patients. It was noted that antidepressant pharmacotherapy reduced bulimic symptoms (14-17), and early neurobiological studies of bulimic patients reported abnormalities that are often present in patients with major depression (18, 19).

The results of recent investigations, however, call into question the existence of a close relationship between bulimia and depression. In this paper we examine the various lines of investigation into this relationship, review the current state of knowledge, and recommend areas for further research.

CLINICAL EVIDENCE

The frequent finding of depressive symptoms in patients who binge and purge has long been noted. Dally (1) reported affective symptoms in a subgroup of anorexic patients with binge/purge behavior. Others (2, 3) have also noted that anorexic patients with bulimic behavior are more frequently given diagnoses of de-

pression and are more suicidal than nonbulimic patients with anorexia nervosa.

Normal-weight patients with bulimia also appear to have a high frequency of suicide attempts and depression. Russell (4) found substantial depression in such patients, with 37% of 30 patients having made previous suicide attempts. Hudson et al. (5) found a similar high rate of suicide attempts (36%) in their 74 low- and normal-weight eating disorder patients with bulimic behavior. Viesselman and Roig (6) described current suicidal thoughts in more than half of their 61 bulimic subjects and noted that 20% had made previous suicide attempts. Others (7, 8) have reported high depression ratings in bulimia.

Numerous investigators, using various diagnostic methods, have described substantial concurrent or lifetime depression in their bulimic subjects. Using the Feighner criteria, Viesselman and Roig (6) found concurrent depression in 79% of their bulimic subjects. Herzog (10) found that 24% of his 55 bulimic patients met the Research Diagnostic Criteria (RDC) for concurrent major depressive disorder, and Walsh et al. (11) noted concurrent RDC major depressive disorder in 30% of their 50 patients with bulimia.

Hudson et al. (5), using *DSM-III* criteria, reported that 59% of the normal-weight bulimic patients they studied and 80% of the anorexic bulimic patients (66% of the total number) experienced major depression sometime during their lives. Among the eating disorder patients with lifetime major depression, the mood disorder preceded the onset of the eating disorder 40% of the time. Using *DSM-III* criteria, Piran et al. (9) reported that 36% of their 33 bulimic patients had had an episode of major depression during their lives. Similar to the finding by Hudson et al., they found that the onset of depression preceded the eating disorder in 44% of these subjects. Walsh et al. (11) found that the lifetime prevalence of major depression in their 50 bulimic patients was 71%, which is similar to the rate reported by Hudson et al. (5).

These prevalence rates are substantially higher than those reported for major depression in epidemiological surveys of the general population (20, 21). While the higher rates of concurrent and lifetime major depression in patients with bulimia suggest a relationship, none of these bulimia studies used a simultaneously interviewed control group. Thus, the findings of depression may have been biased.

Other investigators have noted differences between

Received Aug. 14, 1987; revision received June 20, 1988; accepted Aug. 5, 1988. From the Department of Psychiatry, Ohio State University. Address reprint requests to Dr. Levy, Department of Psychiatry, Ohio State University, 473 West 12th Ave., Columbus, OH 43210.

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the symptoms of depression in bulimia and those in major depression. Johnson-Sabine et al. (22) believe that dysphoric mood in bulimic persons is not primary but is related to the presence of abnormal eating. They observed that dysphoria ratings increased on the days that bulimic subjects engaged in binge/purge behavior. Cooper and Fairburn (23) reported that although bulimic and depressed patients had similar severity of depression ratings on the Montgomery-Asberg Scale (24), discriminant function analysis revealed a difference in symptom pattern.

Looking at the relationship between bulimic and depressive symptoms during a 10-week treatment period, Lacey (25) reported that as the frequency of bulimic behavior declined with behavioral and insight-oriented psychotherapy, symptoms of depression actually increased. In contrast, Norman and Herzog (26) found improvement in both eating behavior and depression 1 year after patients' initial evaluations. Swift et al. (27) reported low depression ratings in bulimic patients 2–5 years after initial evaluation despite continued symptoms of bulimia.

There are several caveats in interpreting these varied findings. Investigators may observe the same phenomenon (e.g., worsening of mood on binge days) but differ about what they consider primary. Incomplete descriptions of the characteristics of bulimic patients on follow-up raise additional questions. For instance, although Lacey (25) found that depression increased as bulimic symptoms decreased, it is not known whether the patients with emerging depression were at greater risk for subsequent relapse into bulimia. Furthermore, bulimic patients may manifest symptoms of depression for a variety of reasons. In some instances, depression may be secondary to the abnormal eating behavior and its ensuing psychosocial consequences. Indeed, an apparent high frequency of depressive symptoms in bulimia might to a large degree reflect the fact that "depressed mood and self-deprecating thoughts" were required for the *DSM-III* diagnosis of bulimia. At other times, depressive symptoms may reflect a condition of malnutrition. While the classic study of Keys et al. (28) indicated that food-deprived subjects may develop a variety of depressive symptoms when they lose weight, it is possible that normal-weight but malnourished bulimic patients may suffer similar physiological changes affecting mood. Studies designed to monitor bulimic patients' nutritional status and mood over time would help resolve this question.

We can only estimate the true prevalence of concurrent depression and bulimia in the general population, since there have been no large studies investigating depression in bulimic and control (psychiatric and normal) subjects in which structured interviews were conducted by raters blind to diagnosis. While the prevalence of depression, as determined by nonblind investigators, is much higher in bulimic persons than in the general population, the possibility of bias cannot be totally dismissed. Moreover, samples of bulimic subjects are generally drawn from patients seeking

treatment, which may create a skew toward bulimic subjects with greater depression, and thus the results may not be generalizable to the bulimic population as a whole.

FAMILY STUDIES

Early studies reported an apparently high prevalence of affective disorder in the families of bulimic probands. Pyle et al. (12) studied 34 bulimic patients, some of whom also had a history of anorexia nervosa. According to the patients' self-reports, 16 had at least one first-degree relative with depression. This early study did not use research criteria for making diagnoses of family members, however, and did not use a control group. Lee et al. (8) found that among 56 patients with bulimia (some with a history of anorexia nervosa), 33 reported having a first-degree relative with affective disorder; however, these researchers did not use a control group either. Hudson et al. (13) found possible or probable *DSM-III* major depression in 16% of the relatives of patients with normal-weight bulimia. This exceeded the rates for their comparison groups: bipolar disorder (9%), schizophrenia (2%), and borderline personality disorder (1%). However, the comparison groups were not assessed simultaneously with the bulimic subjects, and the criteria used to delineate "possible" major depression were unspecified. In an uncontrolled sample, 61% of the bulimic patients studied by Piran et al. (9) reported a family history of depression. In a comparison of 15 women with normal-weight bulimia and 15 sex-matched control subjects, however, Weiss and Ebert (29) found no significant difference in the number of psychiatric hospitalizations between the bulimic and control women's families. Musisi and Garfinkel (30) compared 20 bulimic patients, some of whom had a history of anorexia nervosa, with 20 normal control subjects. Only one bulimic proband had a first-degree relative with major affective disorder, compared with two of the control subjects.

The results of these studies suggest that when a normal control group is simultaneously examined, the apparently high prevalence of affective disorder in the families of bulimic probands tends to disappear. These data need to be evaluated cautiously, however, because in none of the studies we have mentioned were the interviewers who made the diagnoses of family members blind to the probands' diagnoses.

Stern et al. (31) determined the lifetime prevalence of affective disorder in the first- and second-degree relatives, excluding children, of 27 normal-weight bulimic women and 27 women with no histories of eating disorders. Diagnoses of family members were made by interviewers blind to the probands' diagnoses. The authors found that the prevalence of affective disorder was 9% in the relatives of the bulimic probands and 10% in the relatives of the control probands. They also found no difference between the two groups when the comparison was limited to first-degree relatives, to

mothers, or to probands with at least one affectively ill first-degree relative.

These findings suggest that normal-weight bulimic patients probably do not, as a group, have a greater familial prevalence of affective disorder. There may, however, be a relationship between family history of depression and certain characteristics of bulimia. Lee et al. (8) found that bulimic patients with positive family histories of depressive spectrum illnesses had earlier onset of bulimia. Mitchell et al. (32), comparing bulimic subjects with and without family histories of depression, found that patients with positive family histories were more likely to have been treated for depression and to attribute their binge eating to dysphoric symptoms. This relationship was supported by research by Wilson and Lindholm (33), who reported that the more severely depressed bulimic patients were more likely to have a positive family history of depression than the less depressed bulimic patients.

Since all positive family history studies use either the probands' self-reports or, less often, nonblind interviews, the prevalence of familial depression is difficult to interpret because of possible bias. Carey et al. (34) discussed the necessity of control groups in family studies. Even studies that use population rates or compare rates of groups studied at another time may be flawed by differences in time, place, sampling, and possible bias in expected outcome.

The only study in which mothers of bulimic probands and control subjects were interviewed by psychiatrists blind to probands' diagnoses (31) did not find a difference in family history of depression. Additional studies using structured interviews and blind family interviews of bulimic, depressed, and normal probands are needed for accurate identification of real similarities and differences.

PHARMACOTHERAPY WITH ANTIDEPRESSANTS

Tricyclic antidepressants and monoamine oxidase inhibitors have recently emerged as effective treatments for bulimia (14-17, 35, 36). In their double-blind study, Pope et al. (14) found that imipramine-treated bulimic patients had a significantly greater reduction in binge frequency and depression, as measured by the Hamilton Rating Scale for Depression (37), than did placebo-treated bulimic patients. It is not clear whether the reduction in depressive or bulimic symptoms was limited to the bulimic patients with concurrent major depression.

In a double-blind study, Walsh et al. (16) found that bulimic patients treated with phenelzine had significantly fewer binges per week and lower scores on the Eating Attitudes Test (38) than patients given placebo. While the patients were categorized as either depressed or nondepressed in that study, diagnoses of depression were not made, nor were the criteria for the depressed category stated. At the end of the study, there did not appear to be any differences in severity of depression

between the phenelzine-treated patients and the control subjects or between the depressed and nondepressed bulimic patients. The relative absence of substantial depression in the study sample may have accounted for the lack of differences in Hamilton depression scores.

In their double-blind study, Hughes et al. (17) reported that bulimic patients treated with desipramine decreased their number of binges per week by 91%, whereas placebo-treated bulimic patients had 19% more binges per week than at the beginning of the study. Placebo nonresponders decreased their binge eating by 84% when they were crossed over to treatment with desipramine. Patients taking the active drug also had a significantly greater reduction in severity of depression, as measured by the Zung scale, than those taking placebo. Since no patient in the sample had a concurrent major depression, this reduction in self-rated depression was probably due to the improvement in well-being noted by the patients whose bulimia had responded to treatment, rather than to a response to treatment of a mood disturbance, although a possible direct effect on dysthymic symptoms cannot be excluded.

Agras et al. (35), who studied 20 bulimic women, reported that imipramine reduced binge and purge behavior significantly more than placebo. While concurrent depression diagnoses were not reported, the imipramine-treated bulimic subjects experienced a significantly greater reduction in Beck Depression Inventory ratings than did the patients taking placebo.

In a double-blind crossover study, Kennedy et al. (36) found that isocarboxazid-treated bulimic patients had significantly greater reductions in binge eating, purging, severity of depression (as measured by the Hamilton and Beck scales), and Eating Attitudes Test scores than did placebo-treated women with bulimia. It was not specified whether the bulimic patients with concurrent major depression had a different response from that of the patients without concurrent illness.

Mitchell and Groat (15) reported less clear-cut findings in their double-blind, placebo-controlled trial of amitriptyline in bulimic subjects. Both amitriptyline-treated and placebo-treated subjects had significant reductions in binge eating during the study. Those taking the active drug, however, had a significantly greater reduction in Hamilton depression scores than those taking placebo. When the bulimic subjects were divided into depressed and nondepressed groups (by means not defined), the nondepressed bulimic subjects had a reduction in binge eating whether they were taking drug or placebo. The depressed bulimic subjects treated with placebo did not reduce their binge eating or depression. Depressed bulimic subjects treated with amitriptyline, however, had a partial antibinge response, and their Hamilton depression rating dropped to the nondepressed level. The bulimic subjects in Mitchell and Groat's sample were more depressed than those in other studies, with a mean Hamilton score of about 20. At least 20% had concurrent affective disorders, but the authors suggested that this prevalence

may have been inaccurate, since they initially tended to underdiagnose depression in bulimic patients. Another difference between this study and others is that the subjects had come to the clinic for treatment, rather than responding to an advertisement as in other studies (14, 16, 17), and may have been more motivated. Thus, this study appears to suggest that nondepressed bulimic patients who seek treatment have a high placebo response rate, whereas depressed patients with bulimia may be more difficult to treat and may require an active drug rather than placebo.

In the only study of antidepressants in bulimia that produced negative results, Sabine et al. (39) found that neither mianserin nor placebo was helpful. The dose of mianserin they used was less than the dose recommended for the treatment of depression, however, and thus may have been inadequate for bulimia as well. The same problem may have affected the study by Mitchell and Groat (15), since blood levels of the antidepressant were "subtherapeutic" in half the patients in whom concentrations were measured. The importance of adequate dosing was supported by the study by Hughes et al. (17), who found that of six nonresponders to desipramine who had subtherapeutic blood levels (<125 ng/ml), four attained complete remission when the dose was appropriately increased. Whether the therapeutic blood level necessary to treat depression is the same as the level necessary to treat bulimia is an unresolved question. Moreover, it is unclear whether therapeutic levels are more important in treating depressed than nondepressed bulimic patients. Further research with antidepressants and monitoring of blood levels in depressed and nondepressed bulimic patients will be necessary to evaluate this issue.

POLYSOMNOGRAPHY

Characteristic sleep abnormalities, including shortened REM latency, increased REM density, and decreased delta (slow wave) sleep, have been reported in adults and adolescents with major depression (40–43). Early reports (18, 44) suggested that some bulimic patients might have shortened REM latencies. Katz et al. (18), in a study of 17 women with bulimia who were in various stages of recovery from anorexia nervosa, found that these women had shorter REM latencies than the control subjects did. All of their subjects with shortened REM latencies (<60 minutes), however, had Hamilton depression ratings higher than 30, indicating the presence of severe depression. Hudson et al. (44), when they presented preliminary findings, reported that bulimic patients had shorter REM latencies than did control subjects; however, when their sample size was expanded, this difference disappeared (45).

More recent investigations have found no significant differences between the polysomnograms of bulimic patients and those of age-matched control subjects (46–48). Walsh et al. (46) investigated the sleep EEGs of 16 bulimic women and found REM latencies and

densities similar to those of normal control subjects. No relationship could be found between severity of depression, as measured by the Hamilton scale, and any EEG variable; however, the density of the first REM period was not assessed. There was a nonsignificant trend for the bulimic patients with concurrent diagnoses of major depression to have shorter REM latencies than those who were not depressed.

Levy et al. (47) found no polysomnographic differences between nine bulimic women and 10 healthy control subjects. None of the subjects had concurrent endogenous major depression, a diagnostic point not clarified in the Katz et al. and Walsh et al. studies. Levy et al. (48) reported a positive relationship between severity of depression and density of the first REM period in bulimic women, even though there was no association between severity of depression and overall REM density.

REM density has been found to be related to severity of depression among patients with major depression (42, 49). Moreover, Kupfer et al. (43) found that the density of the first REM period was greater in younger depressed patients than in control subjects, whereas the other REM episodes were indistinguishable from those of the control subjects. Thus, density of the first REM period may correlate with severity of depression even though it may not be a very good diagnostic marker for major depression.

A relationship between severity of depression and REM latency does not appear to exist. Feinberg and Carroll (49) found that REM latency was shorter in patients with endogenous depression than in those with nonendogenous depression even after the researchers controlled for severity and age.

It appears that nondepressed bulimic subjects, especially those without endogenous depression, have sleep EEGs comparable to those of age-matched control subjects. Thus, in the absence of depression, bulimic patients do not have sleep abnormalities similar to those seen in patients with major depression.

NEUROENDOCRINE FINDINGS

Early studies that investigated the results of various neuroendocrine tests of bulimic patients revealed abnormalities similar to those previously noted in patients with major depression. The dexamethasone suppression test (DST), which produces abnormal results in patients with melancholic or endogenous depression (50–51), has been found to produce abnormal results in subjects with bulimia as well (19, 30, 52–58).

Five uncontrolled studies (19, 53, 54, 56, 58) found that 35%–67% of their bulimic subjects had abnormal results on the DST. Gwirtsman et al. (19) found abnormal DST results (cortisol >5 μ g/dl) in 67% of 18 bulimic patients. Mitchell et al. (53) found that 50% of 28 bulimic outpatients had abnormal DST results, and Lindy et al. (54) found that 35% of 55 bulimic outpatients were DST nonsuppressors. Neither the Gwirts-

man et al. study nor the Mitchell et al. study found a relationship between diagnosis or severity of depression and DST status; however, nonsuppressors in the Mitchell et al. study were more likely to report a family history of treatment for depression for first-degree relatives. Perez et al. (58) reported DST abnormalities in 58% of their 33 bulimic outpatients. Contrary to earlier studies, however, they found a significant relationship between nonsuppression and concurrent major depression (subtype unspecified) but found no relationship between a positive result on the DST and a family history of depression.

Four DST studies (30, 52, 55, 57) have compared bulimic individuals to normal and/or psychiatric control groups. Hudson et al. (52) found that 47% of their 47 bulimic outpatients had DST nonsuppression, compared with 9% of the normal age-matched control subjects. Kiriike et al. (55) reported abnormal DST results in 63% of eight bulimic patients, compared with 11% of normal control subjects. These control subject rates are similar to the rate described for control subjects by Carroll et al. (50). Musisi and Garfinkel (30) found only a 20% prevalence of DST nonsuppression in a largely outpatient bulimic sample (20 patients) compared with 75% of melancholic depressive patients and 10% of normal control subjects. At least 33%, however, binged less than the twice-a-week frequency required by *DSM-III-R*. Levy and Dixon (57) found that 100% of their eight bulimic inpatients were DST nonsuppressors, compared with none of eight patients with nonendogenous major depression. No associations between DST status and severity of depression were demonstrated in this study or in other controlled studies (30, 52).

Some investigators (53) have found that nonsuppression on the DST in bulimia is associated with familial depression, but others (52, 55, 58) have not. Hughes et al. (56) reported that DST results did not predict response to desipramine, but they noted that six of seven nonsuppressors became normal after successful treatment, a finding also reported in depressed patients (59). Clearly, concurrent major depression is not necessary for the manifestation of nonsuppression on the DST in bulimic subjects.

The hypothalamic-pituitary-adrenal (HPA) axis has been investigated with corticotropin-releasing hormone (CRH) by Gold et al. (60). Eight bulimic individuals who had remained free of binge/purge behavior for 10 days demonstrated ACTH and cortisol responses to CRH similar to those of normal control subjects. This finding is in contrast to the blunted ACTH response to CRH demonstrated in low-weight anorexic patients (60) and inpatients with major depression (61). Women with bulimia have also been found to have normal 24-hour secretions of cortisol (62), unlike the elevated cortisol secretion reported in patients with major depression (63).

Several studies have investigated thyrotropin (TSH), growth hormone (GH), and prolactin levels in bulimia and their response to stimulation. These studies were

prompted by findings that in major depression there was a blunted TSH response to thyrotropin-releasing hormone (TRH) (64, 65), a paradoxical GH release following TRH (64), and diminished prolactin response to TRH (66, 67).

Uncontrolled studies of the TSH response to TRH have yielded conflicting results. Gwirtsman et al. (19) reported a blunted TSH response in eight of 10 bulimic subjects. Mitchell and Bantle (68) found a blunted response in only one of six bulimic patients, and Kiriike et al. (69) found that none of their 10 bulimic patients manifested a blunted TSH response.

Results of controlled studies have been more consistent. Norris et al. (70) reported no differences between bulimic and control subjects in TSH response to TRH, and Levy et al. (71) reported no TSH blunting in their nine bulimic and eight control subjects.

Several investigators (19, 67, 68) have found that the TSH response to TRH is delayed up to 50% of the time in bulimia. This contrasts with the pattern in depression, in which the TSH response to TRH is characteristically blunted but rarely delayed (65).

Basal GH level and GH response to TRH are abnormal in some bulimic individuals. Gwirtsman et al. (19) reported that two of three bulimic patients had a paradoxical GH response to TRH. Mitchell and Bantle (68) found this pattern in four of six patients with bulimia, and Muhlbauer and Ziolkowski (72) noted a similar GH response in two of four bulimic patients.

Kiriike et al. (69) reported that three of 10 bulimic patients had a high basal GH level, and two of 10 showed an abnormal response (more than 4 ng/ml over baseline). In the only controlled study to date, Levy et al. (71) found that normal-weight bulimic patients had a significantly greater mean basal GH level and a greater GH response to TRH than did control subjects. This GH profile is distinct from that of depressed patients, in whom the basal GH level is normal (73) but GH response to TRH is sometimes present (64) and sometimes not (73). A further distinction between bulimia and depression lies in the GH response to clonidine, which has been reported to be normal in bulimic subjects (74) but blunted in depressed patients (75).

Prolactin has only recently been investigated in bulimic patients. In their uncontrolled sample, Kiriike et al. (69) reported a normal basal prolactin level and a normal physiological prolactin response to TRH. Levy et al. (71), in contrast, found that bulimic subjects had significantly lower basal prolactin levels than did age-matched control subjects, and there was a trend toward their having a greater prolactin response to TRH than did the control subjects. The findings of these studies contrast with the findings of most (66, 67) but not all (76) investigations, which show a blunted prolactin response to TRH in depression.

Whether bulimic and depressed patients differ in their gonadotropin response to stimulation is not clear. Uncontrolled studies of fertile women with depression have revealed possibly low basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels but

TABLE 1. Summary of the Literature on Endocrine Profiles in Bulimia and Major Depression^a

Endocrine Profile	Bulimia	Major Depression
Basal GH level	↕	Normal
Basal prolactin level	↕	↕
GH response to clonidine	Normal	↕
GH response to TRH	↑	↑/Normal
Prolactin response to TRH	↑	↓
TSH response to TRH		
Blunted	No	Yes
Delayed	Yes	No
Basal LH level	↓	Normal
LH response to LH-RH	↑	Normal
24-hour cortisol level	Normal	↕
ACTH response to CRH	Normal	↕
DST result	Nonsuppression	Nonsuppression

^a None of the studies used for this summary reflects a direct comparison between subjects with bulimia and those with major depression. When possible, controlled studies were used in compiling data.

a normal response to luteinizing hormone-releasing hormone (LH-RH) (59). In a controlled study, Amsterdam et al. (77) found similar basal gonadotropin levels and similar LH and FSH responses to LH-RH in depressed and normal fertile women. Thus, this axis appears generally normal in fertile depressed patients. Levy et al. (78) found that bulimic patients had lower basal LH levels but a greater response to LH-RH than did control subjects. If replicated, this finding would identify a further neuroendocrine distinction between bulimia and depression.

The neuroendocrine system, while disturbed in normal-weight women with bulimia, is unlike that described in depressed subjects, with the possible exception of the HPA axis (table 1). Recent findings in bulimic patients of elevated β -hydroxybutyric acid (79), enlarged ventricles on CT scans (80), and the failure of an elevated GH level to result in elevated somatomedin C (81) support the possibility that malnutrition may contribute to the endocrine abnormalities observed in bulimic individuals.

CONCLUSIONS

While many bulimic patients are depressed, a preponderance of the evidence suggests that bulimia is not a variant of depression. Clinical studies of depression in bulimia have consistently identified concurrent depressive symptoms or diagnoses of depression. However, the raters who made the concurrent diagnoses in these studies were aware of the primary eating disorder diagnoses, which may have biased the outcomes.

Response to antidepressant medication does not constitute confirmation of the relationship between depression and bulimia: The response of panic disorder (82), school phobia (83), and enuresis (84) to antidepressants indicates that these agents treat a broader

spectrum of disorders than just depression. As Brotman et al. (85) have indicated, some patients experience only an antibinge effect from an antidepressant, whereas others experience only an antidepressant effect.

Currently available sleep EEG and neuroendocrine studies, with the possible exception of the DST, appear to distinguish major depression from bulimia. The meaning of an abnormal endocrine test result is not clear. Neuroendocrinopathies in bulimic women have not been found to correlate with depression (54, 55, 58, 69), and Hughes et al. (56) did not find that DST results predicted response to desipramine. The possibility of a relationship between neuroendocrine abnormalities and familial depression has been raised (54) but remains controversial (53, 57).

There is inadequate support for the previously suggested association between bulimia and depression. To date, properly designed polysomnographic and family history investigations have failed to find differences between bulimic and control samples.

The importance of concurrent depression or a family history of depression for a bulimic patient is not yet established. It is possible that bulimic patients with family histories of depression are at greater risk of developing depression (32). Moreover, bulimia with concurrent depression may be more difficult to treat (15).

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Dangerousness and the Civil Commitment Process

An Empirical Comparison of the Stone and Dangerousness Criteria for Civil Commitment

Steven K. Hoge, M.D., Paul S. Appelbaum, M.D., and Alexander Greer, J.D., M.A.

Massachusetts civil commitment criteria were compared in an emergency setting with a set of criteria developed by Dr. Alan Stone. Contrary to expectations, the Stone criteria proved to be more restrictive in a sample of 503 patients. Few patients would be newly committable under the Stone criteria; of the 35 patients committable under the Stone standard, 32 also met the current Massachusetts criteria for commitment. The clinical and policy implications of the adoption of the Stone criteria are discussed.

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Civil commitment laws have undergone dramatic revision in the last 15 years. Before 1969 the standard for involuntary hospitalization in most jurisdictions was one of “need for treatment” (1). At that time California adopted a new standard stipulating that a patient must be dangerous to self or to others or gravely disabled in order to be committed (2). Almost every state has since passed similar laws (3).

These changes were made, in large part, at the insistence of reformers who were concerned about the implications for civil liberties of prolonged institutionalization on vague grounds of “need for treatment.” *Parens patriae* justifications for civil commitment—which emphasized the benevolent intent of the state to

offer treatment to those in need of care—were rejected in favor of police power justifications that restricted the legitimate scope of commitment to “dangerous” patients. Psychiatrists have protested the emphasis that the new standards place on dangerousness as detrimental to the traditional role of physicians as care givers (4, 5). It is argued that the new laws require psychiatrists to act as agents of social control, a task for which they are ill-suited, and undermine the fiduciary basis of the doctor-patient relationship. Furthermore, many persons in need of treatment, yet unable by virtue of their mental illness to acknowledge that need, do not qualify for commitment under the new standards, leaving them without any possibility of receiving care. Recent concern about the homeless mentally ill has highlighted this issue (6).

In response to the criticisms of dangerousness-oriented commitment criteria, Alan Stone proposed a modified set of treatment-oriented criteria designed to address some of the major concerns of civil libertarians, yet restore the paternalistic approach of the earlier statutes. The following five requirements must be met under the Stone criteria before a patient can be committed: 1) a reliable diagnosis of severe mental disorder must be made, 2) the immediate prognosis for the patient must be one of major distress, 3) an effective treatment must exist, 4) the patient must offer an incompetent refusal of treatment, and 5) the proposed treatment must meet a test of reasonableness, i.e., it must be such that a reasonable person in the same situation would accept the proposal (5).

The Stone commitment criteria later formed the basis for APA’s widely discussed Model Law on Civil Commitment (7). The latter, unlike Stone’s original proposal, retains a modified version of traditional criteria for dangerousness, but it adds a treatment-oriented criterion focused on patient distress and deteri-

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oration and requires evidence of incompetence to decide on treatment. To date, no jurisdiction has adopted either the Stone or APA criteria in toto, in part due to apprehension that movement away from sole reliance on dangerousness standards would dramatically increase the number of people susceptible to commitment—an outcome opposed on both civil libertarian and economic grounds. Durham, for example, found that when existing dangerousness standards in the state of Washington were broadened to include those patients suffering “severe deterioration in routine functioning,” involuntary hospitalization nearly doubled. This unexpectedly large influx of patients, representing a new segment of the population, overwhelmed the psychiatric delivery system (8). Durham and Lafond argued that these data should encourage caution in other states that are considering similar changes in their commitment laws (9).

Only one previous attempt has been made to estimate the likely impact of implementing Stone’s criteria as a whole, rather than (as in Washington State) merely adding a provision to an existing dangerousness-oriented law allowing commitment of those facing severe deterioration. Monahan et al. (10) analyzed a set of committed patients in California, assessing their probable committability under the Stone criteria. They found that only 46% of the patients in California who were committed in an emergency setting would also meet the Stone standards, compared with 84% of patients recommitted after a 3-day hold. The study did not address, however, the complementary question of how many patients who were not committed under the California statute might have been committed under the Stone proposal, thus limiting the authors’ ability to assess the proposal’s overall effect. In addition, the nature of the California commitment process led to difficulties in the determination of which patients met Stone’s criterion of incompetent refusal of treatment.

This study was designed to address prospectively the question of what effect adoption of the Stone (or closely related) criteria would have on the number of patients admitted to and excluded from a mental health system.

METHOD

The study was conducted at the Emergency Mental Health Service of the University of Massachusetts Medical Center, which provides emergency evaluation, screening, and referral services for the Greater Worcester Community Mental Health Center and similar services to patients referred from much of central Massachusetts. Resident psychiatrists of the emergency service responsible for making commitment decisions were asked to fill out, after each patient assessment, a 27-item questionnaire dealing with patients’ committability under current statutes and under the Stone criteria. Stone’s original description of his criteria (5, pp. 66–69) was made available in the emergency room and

was reviewed with the staff before the initiation of the study. Data regarding diagnoses and demographic characteristics were also gathered.

Missing data points have been excluded from individual analyses; cited percentages reflect the corrected sample size.

RESULTS

Examining psychiatrists returned 503 questionnaires representing 56% of total patient visits over the span of the study. Demographic characteristics of this sample were compared to a 20% random sample of all patients seen during the study period. Patients for whom questionnaires were returned were more likely to have been hospitalized than the random sample ($\chi^2=4.21$, $df=1$, $p<0.05$); there were no statistically significant differences in sex, race, age, and primary diagnoses (schizophrenia versus others) between the two groups. Thus, although the sample was enriched with hospitalized patients, it was otherwise representative of the broader emergency room population.

Fifty-two percent ($N=256$) of the patients were male (some percents reported are based on an N of less than 503). The sample was overwhelmingly white (94%, $N=447$), with small proportions of Hispanic (4%, $N=20$) and black (2%, $N=10$). The mean \pm SD age was 33.2 ± 13.5 years. Affective disorders accounted for 34% ($N=168$) of the primary diagnoses in the sample, schizophrenic disorders for 22% ($N=106$), personality disorders for 15% ($N=75$), substance abuse disorders for 15% ($N=75$), organic disorders for 2% ($N=11$), and other disorders for 12% ($N=58$). Forty-seven percent ($N=193$) of the patients were psychotic at the time of presentation. The majority of patients (65%, $N=325$) lived in unsupervised settings, 15% ($N=76$) lived in supervised dwellings, 10% ($N=50$) lived in shelters, 6% ($N=31$) were homeless, and 0.6% ($N=3$) were in jail (data were missing for 3.4% of the patients).

Massachusetts Commitment Criteria

The Massachusetts statute permits involuntary hospitalization when a person presents a “substantial risk of physical harm” to self or others or is “unable to protect himself in the community” by reason of mental illness (11). (For the sake of simplicity we shall employ the California terminology of “gravely disabled” for the latter category.)

Examining psychiatrists indicated that 59% ($N=296$) of the total sample met at least one of the Massachusetts commitment criteria. This large group (group 1) defines the outer parameter of the state’s coercive power to hospitalize but probably overstates the true scope of the commitment statute in practice. Many of these patients accepted hospitalization voluntarily (and might have even in the absence of the threat of involuntary commitment) or accepted other treat-

TABLE 1. Massachusetts Criteria for Civil Commitment Met by 503 Emergency Room Patients

Criteria Met	Total Sample (N=503)		Patients Who Did Not Accept Treatment (N=83)	
	N	%	N	%
One criterion				
Dangerous to self only	94	18.7	8	9.6
Dangerous to others only	20	4.0	5	6.0
Gravely disabled only	53	10.5	15	18.1
Two criteria				
Dangerous to self and to others	20	4.0	4	4.8
Dangerous to self and gravely disabled	46	9.1	8	9.6
Dangerous to others and gravely disabled	34	6.6	9	10.8
All three criteria	29	5.8	8	9.6
Any criterion	296	58.8	57	68.7

ment that averted hospitalization altogether. An alternative estimate of the number of patients most likely to be involuntarily hospitalized involved construction of a second group (group 2) that was drawn from patients who did not accept recommended treatment and who also met at least one of the Massachusetts criteria. This resulted in a sample of 57, or 11% of the total population. Just as group 1 overestimates the number of patients subject to truly coercive hospitalization, group 2 probably understates that figure by failing to take into account those patients whose acceptance of recommended treatment was based on their knowledge that they might otherwise be subject to commitment.

The specific criteria for commitment met by patients in each group can be found in table 1. "Dangerous to self only" was the largest subgroup of committable patients from the population as a whole (18.7%), whereas "gravely disabled only" was the largest subgroup (18.1%) of committable patients from the group that did not accept treatment.

Stone Commitment Criteria

The Stone criteria for commitment met by the total sample are summarized in table 2.

Of the total population, 76% (N=383) were rated as suffering from a severe mental disorder. These patients were described as psychotic in 47% (N=193) of the cases.

Psychiatrists were asked to rate the degree of imminent distress as none, minor, moderate, or major. Patients were rated as suffering from major distress in 54% of cases (N=271), moderate in 32% of cases (N=160), minor in 11% (N=53), and none in 3% (N=13).

The type of distress likely to be endured was subcategorized according to the model suggested by Stone. Twenty-five percent of the patients (N=124) were assessed as having an immediate prognosis for severe anxiety; 26% (N=131), severe depression; 34%

TABLE 2. Stone Criteria for Civil Commitment Met by 503 Emergency Room Patients

Criterion Met	N	%
Severe mental disorder	383	76.1
Immediate prognosis of major distress	271	53.9
Effective treatment available	437	86.9
Response to treatment offer		
Rejection	65	12.9
No response	18	3.6
Incompetent ^a	38	60.3
Reasonable person would accept offer		
Definitely	338	70.0
Probably	145	30.0
All criteria	35	7.0

^aCompetency data refer only to those who refused treatment.

(N=171), severe personality deterioration; 44% (N=221), physical damage to self; and 25% (N=128), other distress. (Patients could be rated as likely to suffer distress in more than one area.)

Effective treatment at the receiving facility was thought to exist for 87% of the patients (N=437).

Patients accepted offered treatment in 83% of the cases (N=401), rejected treatment in 13% of cases (N=65), and did not respond in 4% (N=18). When patients rejected treatment, the examining psychiatrist indicated whether the refusal was related to the patient's mental disorder, Stone's criterion for incompetency. Of the 65 patients who refused treatment, 60% (N=38) were thought to be incompetent according to this standard.

Psychiatrists were asked to rate whether, in their opinion, a reasonable person would accept treatment in the patient's situation. In no case did the evaluator believe that a reasonable person would not accept the offered treatment. In 70% (N=338) of cases the evaluators felt that a reasonable person would definitely accept the treatment; in 30% (N=145) they felt that a reasonable person would probably accept treatment.

In our sample, 7% (N=35) of patients met all the Stone commitment criteria, thus qualifying for commitment under the Stone proposal. In this analysis, missing data points were assumed to represent the absence of the criterion in question, which we believe accurately reflects clinicians' intentions in scoring the forms. When a second analysis was performed in which missing data points were scored as positive, it resulted in the addition of two subjects to the group that met all the Stone commitment criteria. Thus, missing data points did not significantly affect the size of this group. These patients' demographic and residential characteristics are compared with those of the Massachusetts commitment group in table 3.

To demonstrate the effect of each of the Stone criteria on the number of committable patients, each Stone criterion was removed in turn and the number of committable patients was recalculated. The deletion of severe mental disorder resulted in 36 committable patients; the deletion of effective treatment, 36; reasonable person, 35; and major patient distress, 44. The

TABLE 3. Diagnoses and Residences of Patients Committable According to the Massachusetts and Stone Criteria

Characteristic	Massachusetts Group				Stone Group	
	Total Sample (N=296)		Patients Who Did Not Accept Treatment (N=57)		(N=35)	
	N	%	N	%	N	%
Diagnosis^a						
Substance abuse	28	9.5	7	12.3	3	8.6
Affective disorder	109	37.8	18	31.6	10	28.6
Schizophrenia	64	21.6	14	24.6	12	34.3
Personality disorder	45	15.2	6	10.5	1	2.9
Organic disorder	5	1.7	1	1.8	1	2.9
Other	38	12.8	10	17.5	7	20.0
Presence of psychosis	158	53.4	38	66.7	31	88.6
Residence^a						
Unsupervised	188	63.5	36	63.2	21	60.0
Supervised	46	15.5	8	14.0	7	20.0
Shelter	30	10.1	7	12.3	4	11.4
Homeless	21	7.1	6	10.5	3	8.6

^aData were not available for all subjects for all variables.

effect of incompetent refusal is more difficult to judge because the criterion as stated by Stone merges two factors, refusal and incompetence. Since we have incompetence ratings only on patients who refused treatment, we can estimate the effect of eliminating incompetence as a requirement—which leaves 44 patients committable—but not of eliminating refusal. When the two most restrictive criteria—major patient distress and competency—are both removed, 67 patients are committable.

Comparisons Between the Massachusetts and the Stone Criteria

The Stone criteria proved to be substantially narrower in scope than the Massachusetts criteria. Almost all patients committable under the Stone standard (32 of 35 patients) also met Massachusetts commitment criteria (both group 1 and group 2). On the other hand, of the 296 patients committable under Massachusetts law (group 1), only 11% (N=32) would still be committable according to the Stone proposal. Even if one limits the comparison to those patients who also rejected recommended treatment—perhaps a fairer test because they represent those most likely to be committed—of the 57 patients likely to be committed in Massachusetts, only 56% (N=32) would still face commitment under the Stone criteria.

To further explore the effect of a switch from Massachusetts' dangerousness-based criteria to Stone's avowedly paternalistic standard, those patients now committable in Massachusetts (group 1) who would no longer be committable under Stone's proposal were compared with those who would still be committable. The latter were more likely to be psychotic ($\chi^2=16.44$, $df=1$, $p=0.001$), meet statutory criteria for grave disability ($\chi^2=18.30$, $df=1$, $p<0.0001$), be predicted to

suffer severe personality deterioration ($\chi^2=5.82$, $df=1$, $p<0.02$) and to be rated as causing major distress to the community ($\chi^2=9.01$, $df=1$, $p<0.003$) and to their families ($\chi^2=4.46$, $df=1$, $p<0.04$). This group was also less likely to suffer from personality disorder as a primary diagnosis ($\chi^2=4.13$, $df=1$, $p<0.05$) and to meet the statutory criterion for dangerousness to self ($\chi^2=4.20$, $df=1$, $p<0.05$). The two groups did not differ with regard to age, sex, race, residence, presence of severe anxiety or depression, physical damage to self, or other distress.

A similar comparison was performed between the smaller set of patients who were committable under Massachusetts law and did not accept recommended treatment (group 2) and the patients who would not be committable. Those patients who would still be committable were more likely to be psychotic ($\chi^2=14.30$, $df=2$, $p<0.001$), meet the statutory criterion for grave disability ($\chi^2=11.2$, $df=1$, $p<0.001$), and be rated as causing more family distress ($\chi^2=9.11$, $df=3$, $p<0.03$). In response to offered treatment, they were more likely not to respond ($\chi^2=11.77$, $df=1$, $p<0.0001$). This group was also less likely to be given a primary diagnosis of personality disorder ($\chi^2=4.88$, $df=1$, $p<0.03$). The groups did not differ significantly on the degree of community distress, severe anxiety or depression, personality deterioration, physical damage to self, other distress, or sex, age, race, or residence. In sum, both comparisons suggest that implementation of the Stone criteria would restrict civil commitment to a more seriously ill and incapacitated group.

Only three patients were committable under the Stone criteria but not by the dangerousness standards. This small number did not permit statistical analysis. Interestingly, none of these patients was hospitalized in actuality under a system employing dangerousness criteria.

Patients who met the Stone criteria were not distributed randomly across the groups of patients who met the different Massachusetts commitment criteria (group 1, $\chi^2=49.31$, $df=6$, $p<0.0001$; group 2, $\chi^2=16.42$, $df=6$, $p<0.02$). Within group 2, the Stone group was concentrated heavily among those rated as gravely disabled, accounting for more than 72% (N=29) of this subgroup. In contrast, only 21% (N=3) of the remainder—those meeting "dangerous to self" and "dangerous to others" criteria—would be committable under the Stone proposal.

DISCUSSION

The Scope of the Stone Criteria

Commentators have assumed that the Stone model and the related APA Model Law on Civil Commitment would have a broader sweep than current dangerousness standards for commitment (12, 13). Our study found that, contrary to this expectation, the Stone cri-

teria are more restrictive, even if one limits the comparison to patients meeting the current statutory criteria who do not accept treatment—a requirement that probably leads to some underestimation of the true application of coercive hospitalization at the present time. A large number of currently committable patients are excluded from commitment, while few additional patients are added.

How does one reconcile our findings with the prior expectation that the Stone criteria would increase the scope of commitment? The restrictiveness of the Stone criteria in this study, particularly when compared with the treatment-rejecting group (group 2) of patients committable under Massachusetts criteria, is largely a function of the criteria of major patient distress and incompetence. The impact of these factors has clearly been underestimated by both proponents and opponents of the Stone model. Durham's data from Washington were obtained in a very different statutory context, which lacked either of these criteria and retained dangerousness criteria (8, 9). Although Monahan et al.'s earlier study (10) of the Stone model found similar limitations on the number of committable patients in an emergency setting, the reduction was attributed to patients' failure to meet the severe mental illness criterion. The discrepancy between our data and theirs may be due, in part, to some differences in our methodologies. Monahan et al. restricted the definition of severe mental disorder to psychosis, whereas we allowed our respondents to rate each of those variables separately, which we believe is closer to Stone's original intent. In addition, Monahan et al. had data on subjects' responses to initial precommitment treatment offers in less than 25% of the cases. They extrapolated from the determinations of competency made in these cases to arrive at an estimate that 89.3% of their initial commitment sample was incompetent. It seems likely that this led to an overestimate of the rate of incompetent refusal of treatment, perhaps because competent responses to treatment offers went disproportionately unrecorded, since they would lend no support to a commitment petition.

At the time that Stone formulated his model, he believed that the requirement of efficacious treatment would be the most restrictive criterion (A. Stone, personal communication). Examining psychiatrists in our study, however, found that nearly all (87%) of the patients could be effectively treated and this was one of the least restrictive criteria. The relative unimportance of this factor perhaps reflects the relatively recent shift in emphasis in treatment to biological modalities. It may be that psychiatrists had in mind the alleviation of psychotic symptoms with neuroleptics rather than more comprehensive psychosocial adjuncts that Stone may have envisioned.

Our findings indicated not only that many currently committable patients would be uncommittable under Stone's scheme, but also that few patients now uncommittable would be added to the system. This result contradicts assumptions that large numbers of patients

who are in need of treatment and are not now receiving care because of the restrictiveness of current commitment laws would be hospitalized under the Stone model. Rather, the data suggest two possibilities; either 1) the patients in question are now not committable, but the majority of them would be adjudged to be not suffering major distress or to be competent to refuse hospitalization and thus would continue to escape commitment even under the Stone model, or 2) most of these patients are currently committable, but nonstatutory limitations are primarily responsible for their failure to be committed under current law, i.e., they are not hospitalized because they avoid contact with the mental health system or because sufficient beds to accommodate them simply do not exist. An implication of the latter possibility is that structural changes in the mental health system, rather than statutory alterations, may be the most effective means of addressing the problem of the underserved.

Possible sources of bias in our results need to be considered. Monahan et al. (10) have suggested that one source of error in studying commitment laws may be a bias introduced by the influence of current law on referral patterns. It may be that families, police, and social agencies select for presentation to evaluators only those patients likely to meet the existing criteria. An untapped and inestimable pool of patients may emerge from the community when new criteria are introduced. This source of error is less likely to be present in an emergency setting that serves as a major conduit to outpatient treatment as well as inpatient treatment, such as the one studied here. Nonetheless, we cannot eliminate the possibility that there is a segment of the population that does not utilize emergency services that might if the statutes were changed, and thus that some real increase in the number of committable patients might attend the adoption of a Stone-inspired statute.

It is also possible that the application of the Stone criteria in practice may differ from that found in our study. Clinicians making actual commitment decisions and seeking to act in patients' best interests may apply the Stone criteria less rigorously than did the psychiatrists in this study, resulting in more committable patients than predicted. System effects also need to be considered; for example, the judiciary may be more reliant on the judgment of psychiatrists in adjudicating civil commitment cases under a treatment-oriented standard and therefore provide a less effective system of checks and balances than at present, again resulting in an increase in the number of committable patients.

It has also been suggested that Massachusetts may not be typical in the manner in which competency is routinely assessed, and thus that our results may not be generalizable (T. Grisso, personal communication). Recent judicial decisions have made competency assessments commonplace for psychiatrists in the state, and this increased sophistication may have limited psychiatrists' presumed tendency to see all patients who refuse treatment (rather than only 60%, as in this

study) as incompetent (14). Were psychiatrists less circumspect in applying Stone's competency criterion, the size of the net would widen. Yet, if this objection is correct, it suggests that psychiatrists' behavior in this area is amenable to influence by education and experience, and thus overdetermination of incompetency need not be an inevitable result.

The Stone Criteria's Impact on Psychiatry and Social Policy

The data suggest that adoption of the Stone schema would result in dramatic changes in the delivery of psychiatric services. If it were enacted, inpatient units would treat fewer involuntarily committed patients and proportionately fewer patients with personality disorders. As evidenced by the greater rate of psychosis and severe personality deterioration these patients suffer, the community and family distress they cause, and their greater propensity to meet the criteria for grave disability, the mental health system would face a significantly sicker and more disabled population. These increased demands on the system, however, would be offset not only by the smaller size of the committed group, but also by the requirement that effective treatment exist. The Stone model would end commitment of a significant minority of patients now disproportionately represented in the total inpatient census because of their intractability. Inpatient staffs would be freed from the task of managing these untreatable patients and could devote more attention to other patients.

The Stone criteria would also eliminate the problems associated with involuntary hospitalization of the competent patient. Our study indicates that if incompetent refusal of treatment were a requirement for commitment under the present statute, involuntary admissions would be reduced substantially. The legitimacy of interfering in the lives of competent persons, now a matter of legal and ethical concern, would no longer trouble psychiatrists. In addition, adoption of the Stone criteria would limit the dispute over the right of committed patients to refuse treatment by restricting commitment to patients unable to make treatment decisions for themselves. Although each jurisdiction would still have to resolve the questions of who would offer a substitute decision for the patient and by what standard the determination should be made, the likelihood that patients requiring medication would go untreated would be markedly diminished. The Stone criteria would eliminate the curious situation in which competent patients have been granted a right to refuse medication, but not to refuse the arguably more serious deprivation of liberty associated with involuntary hospitalization (9, 10).

The psychiatric delivery system would not be alone in facing change under the Stone criteria. It has been said that civil commitment and the criminal system have significant overlap; the control of deviant behavior is common to both (4). Dangerousness criteria have served to fortify and extend that relationship, and the

replacement of current standards with a more treatment-oriented model may necessitate adjustments in the criminal system. The police and courts would bear greater responsibility for dealing with mentally ill but competent or untreatable persons who have committed or are thought likely to commit violent offenses. Our study suggests that there may be substantial numbers of these patients. Unless current laws are changed, or their use substantially modified, there may be no means of prospective control of their behavior. Society's reluctance to surrender the psychiatric system's capacity to detain dangerous persons, or to embrace an overt system of preventive detention, may constitute the most serious obstacle to legislative endorsement of Stone's approach.

Finally, it should be noted that the method employed in this study, which allows prospective comparisons of the impact of proposed changes in commitment criteria, has its own implications for policy in this area. Most changes in commitment laws have been made to date on theoretical grounds, with little empirical effort made to either anticipate or document their effects. The approach used here offers a simple, inexpensive mechanism for estimating the changes a new commitment law might bring. Although subject to some limitations, as noted earlier, it represents a considerable advance over the current practice of learning about a new statute's effects only in retrospect.

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Commitment: The Consistency of Clinicians and the Use of Legal Standards

Charles W. Lidz, Ph.D., Edward P. Mulvey, Ph.D.,
Paul S. Appelbaum, M.D., and Sarah Cleveland

The reliability and validity of the application of legal criteria for commitment were investigated as part of a larger study. Evaluations of 411 patients by 96 different clinicians showed good interrater reliability for assessment of dangerousness and committability. A strong relationship between ratings of committability and ratings of dangerousness suggests that clinicians were conforming to the logic of the commitment law. Discrepant cases involved patients who desired voluntary admission or whose commitment was completed elsewhere. Results suggest fair application of commitment standards but that two issues of statutory interpretation confused participating clinicians.

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The routine use of civil commitment distinguishes psychiatric care from other medical specialties, and the proper restrictions that should be placed on this professional practice have been the source of continuing controversy. In general, the history of civil commitment in the United States has been a series of swings between rigorous, rule-bound standards and looser, more discretion-based procedures (1, 2). Strict procedural systems have usually led to objections that people needing treatment were not receiving it. Looser standards have usually produced an outcry against the infringements of civil liberties accompanying the application of broad clinical discretion. The 1960s and 1970s saw the most recent swing in this continuing cycle, with the growth of more rigid standards of commitment focused around the notion of dangerousness to self or others.

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The debate about the commitment power can be framed in terms of a widespread discomfort with the justice of commitment's use. What is most often discussed is whether commitment is being used too widely or too narrowly, with the first extreme raising concern about infringement of patients' rights and the second about adequate protection of the community and provision of care for those too disturbed to ask for it themselves. Empirically assessing the justice of any commitment practice would seem, however, to be a futile task. Justice is a value-based, societally relative term, and testing how "just" one practice is in relation to another by operationalizing this notion is an undertaking fraught with conceptual difficulties. Still, without claiming definitively to assess the justice of current commitment practices, it is possible to examine certain empirical evidence relevant to an assessment of the justice of these practices.

Whatever justice might consist of with regard to framing the criteria for committability, a just application of those criteria requires at least that judgments about who should be committed are reasonably reliable and valid (3). To put it differently, the judgment of whether someone is committable should be 1) reasonably independent of the situation in which the judgment is made (e.g., who is making the judgment, when they are making it, and what sort of irrelevant situational factors are involved) (4-7) and 2) closely correlated with the normative standard upon which such decisions are supposed to be made (i.e., the standards contained in commitment law) (8, 9). This paper will present some evidence on how closely clinicians' judgments regarding the committability of patients correlate with each other and how closely they appear to correspond to the legal criteria governing these judgments.

METHOD

The data for this study were collected at a large urban psychiatric hospital that provides services primarily to a geographically defined catchment area. The law in the jurisdiction in which the study was done allowed for individuals to be committed to a psychiatric facility for up to 5 days on an emergency basis if

the individuals were found to be mentally ill and dangerous to themselves or others or incapable of caring for themselves (such that there was imminent danger of loss of life or grave physical harm).

As part of a large descriptive study regarding the determination of dangerousness, observers were placed in the emergency room 24 hours a day, 7 days a week, for a 5-month period. They observed the interviews between clinicians and patients as well as the discussions among clinicians concerning what sort of treatment and disposition options were appropriate. Using a type of speedwriting, observers produced near verbatim transcripts of the interactions they observed. This technique for recording conversations was tested during training and found to be reliable and valid, with observers consistently recording 75% of the content discussed.

Observers' notes of the emergency room interactions were dictated and transcribed into a computer system. Data collected from patients' medical records and copies of case summaries written by the clinicians who saw the patients were also entered into the computerized database. The observers' notes and the background information on the patients were subsequently coded for a wide variety of issues relating to treatment decision making.

In addition, the two hospital staff clinicians (usually a nurse and a psychiatrist) who evaluated the patients performed independent ratings of patients on 12 dimensions using 7-point Likert type scales (see appendix 1). These ratings were done in the emergency room immediately after patients had been assessed. With only a few exceptions, the emergency room clinical staff agreed to be observed and to provide ratings on patients. In all, 96 different clinicians participated in the study and evaluated 411 cases.

For our purposes here, the interrelationships among four of the scales are considered: 1) dangerousness to others, 2) inability to care for self, 3) suicidality, and 4) committability. The questions addressed here are 1) whether there is an acceptable level of reliability in clinicians' judgments of committability, and 2) whether there is the type of consistency among these scales that would be expected if commitment judgments were being made according to the approach laid out in the statute governing this jurisdiction. Each of these questions is central to the continuing debate about the fairness of the implementation of the present system of involuntary commitment.

The strategy for addressing these questions is a combination of quantitative and qualitative techniques. First, the relationships between raters and the particular ratings of interest are examined quantitatively for levels and patterns of consistency. Next, interview notes of those cases that do not fit the expected pattern are examined qualitatively to determine what types of factors might be contributing to any observed inconsistencies.

FINDINGS

Agreement Between Raters

The first question of interest was how reliable different clinicians appeared to be when rating the same patient for dangerousness, suicidality, ability to care for self, and committability. Intraclass reliability coefficients (10) were calculated for each of these scales, and there appeared to be a generally fair to good level of reliability between raters for each of these judgments. R values were as follows: currently dangerous, 0.67; currently suicidal, 0.66; able to care for self, 0.44; and committable, 0.68. This analysis showed that, for all the vagaries of the terms used in commitment statutes, there did appear to be some reasonably well-shared notions among the clinicians about what these terms mean.

Nonetheless, some disagreement did exist among the clinicians regarding these concepts, and it is reasonable to ask what might have caused this disagreement. Two factors are obvious. First, a certain amount of the error is attributable simply to mundane factors present in any use of a set of scales by almost 100 people. In a few cases the clinicians seemed to have simply reversed the ends of the scales. There were also many small discrepancies from a "perfect" association, such as when one rater would assign a value of 6 and the second would assign a 5. Such "error" is not practically important.

Cases of valid, wide disagreement about committability are of interest, however. To ascertain the source of unreliability in these instances, we qualitatively examined the text of cases in which there appeared to be large disagreements about the committability of patients. Since the clinicians rated cases for committability on a scale of 1 to 7, we focused our in-depth qualitative analysis on cases in which one clinician gave the patient a rating of 1 or 2 and the other clinician rated the patient a 6 or 7. This seemed to us to select only the cases in which clinicians held markedly different opinions.

There were 17 cases out of 404 that showed these extreme disagreements (seven patients had only one rater). For each case, the text of the emergency room interview was read closely and the medical record was reviewed. In the overwhelming majority of the cases, the disagreement about committability appeared to fit the same pattern.

In 13 cases, the differences in judgment about committability appeared to reflect a disagreement about whether a patient who desires voluntary admission is committable. All but three of the group either were voluntarily admitted or expressed a desire to be admitted voluntarily. One of the remaining cases involved a disagreement between clinicians about whether or not to accept an already approved emergency commitment from another hospital. Overwhelmingly, these were patients who would have been committed but who brought themselves to the emergency room and were willing to sign themselves in for treatment. In line with

their interpretation of the law's preference for a "least restrictive alternative," some clinicians did not rate these individuals as "committable" because they did not require imposition of the state's authority in order to obtain treatment.

Congruence Between Commitment Standards and Ratings of Committability

The second major question of interest was whether clinicians' judgments about the legal standards and patients' committability showed the relationships that one would expect if clinicians were following the logic of the commitment statute. In other words, do dangerousness to others, suicidality, and inability to care for oneself show a positive and strong relationship to the judgment of committability? This question was attacked quantitatively in two ways.

First, the relationship between the committability rating and a "proxy" standard rating was examined. We refer to the latter variable as the proxy variable because it stands as a proxy for the legal standard of dangerousness as defined by the law in this jurisdiction. The proxy variable was the highest of the three summed scores for dangerousness to others, inability to care for self, or suicidality. We used the sum of the two raters' scores on each of these three ratings to create a scale that ranged from 2 to 14. Those patients rated by both clinicians as being highly dangerous to others, for example, would have a high sum, while those seen as not dangerous would have a low sum. The correlation of this score with the summed committability score thus provided an estimate of the association between the most likely reason for commitment and the committability rating. These two values should be highly associated if any one of the statutorily appropriate standards was seen as present and influential in determining the committability rating.

The correlation between the proxy variable and the committability rating was respectably high ($R=0.707$). While it is possible to argue whether this is as strong a relationship as it "ought" to be, it is clear that a large part of the variance in clinicians' judgments about whether a patient is committable was accounted for by their judgment about how dangerous or unable to care for self the patient is. This analysis would lead one to believe that there is the expected consistency of judgment that the law supposes.

This analysis, however, does not provide an overall view of the relationships that might exist among these judgments. It is possible, for instance, that the procedure of calculating a proxy variable is eliminating from view several important relationships among the three standards and their relationship to committability judgments. Specifically, it is possible that determinations about whether a patient meets each of these standards may be working cumulatively to trigger the committability judgment. For example, patients who are "somewhat" dangerous to others and "somewhat"

suicidal might be considered likely candidates for commitment.

A second quantitative analysis was therefore done to test the strength of different relationships among these ratings. Because the distributions of the values for two of the four ratings were not normal, a log linear approach was taken to test the relationships among the ratings of committability, dangerousness to others, suicidality, and inability to care for self. A 2 by 2 by 2 by 2 logistic analysis showed that the data were best described by a model that included only the direct two-way effects between the ratings for dangerousness to others, suicidality, and inability to care for self and committability (likelihood ratio $[4]=3.90$, $p=0.42$). The inclusion of three-way interactions singularly or in full did not significantly increase the fit of the model. Moreover, the parameters for any of the additional three-way interaction terms were not significant, and a deletion of any one of the two-way effects left the resulting model not significant. Judging from these results, although the notions of dangerousness to others, suicidality, and inability to care for self are not independent of each other, a high rating on any one of them draws a high committability rating. Although there may be some cases in which there is a cumulative effect, this regularity in the data is not large enough to be noticeable.

Although these analyses do provide support for the notion that clinicians are making committability determinations in line with statutory guidelines, it should be remembered that neither of these analyses shows that only patients who actually meet the legal criteria are being committed. We made no attempt to decide whether or not the patients were "really" dangerous to themselves or others or unable to care for themselves. This is not a check on the predictive validity of the clinicians' judgments but rather a test of convergent validity that uses the clinicians' judgments of other elements of the law. It simply shows that, by and large, clinicians' global judgments of committability seem to incorporate some elements of the legal model.

A qualitative analysis was then done to shed light on what might have occurred in cases where the relationship between the ratings of the standards and of committability appeared to be opposite to that expected. In a small but significant number of cases, ratings on the proxy variable were very high and those for committability low, or vice versa. These instances of inconsistency are important not because they account for a substantial part of the "error," although they do (indeed, when the 17 cases we discussed are eliminated from the computation of the correlation, the correlation coefficient rises considerably [$R=0.774$]), but because it is precisely these cases that make an important policy difference. If someone is rated as committable but is not dangerous, that sets the stage for a violation of his or her rights. If someone needs treatment and is dangerous, but is rated as not committable, the method of evaluating and managing this person is defective. It is these situations that deserve additional

scrutiny to determine how the intent of the commitment statute may be subverted.

The first group we looked at were those who scored high on the proxy variable (i.e., a score of 12 or more) and low on committability (a score of 8 or less). Fourteen cases fit this criterion. In each case, the text of the emergency room interview was read closely and the medical record was reviewed.

With two idiosyncratic exceptions, these cases again all fit a single pattern. Although there was only an overlap of two cases between this sample and our previous sample of cases in which clinicians disagreed about committability, all of the cases in this sample also involved patients who would otherwise have been rated as committable except that they brought themselves to the emergency room and were willing to sign themselves in for treatment. Again, differing interpretations about the applicability of the commitment statute to patients who seek treatment voluntarily appeared to be the source of discordant judgments.

The next group we looked at were those who were high on the committability scale (a score of 12 or more) and low on the proxy scale (a score of 8 or less). These, of course, were cases in which the law's requirement for dangerousness or inability to care for self before commitment seemed not to have been met. In these cases, none of the three ratings scored by the two evaluating clinicians was above the midpoint, and yet these same clinicians scored these patients as highly committable.

Only six cases fit this description, and a close examination showed that one of them probably reflected an instance in which the rating scales were misused. In this case, one of the clinicians probably reversed the scale for dangerousness, since she described the patient as very dangerous when talking with the attending physician but then rated the patient at the very bottom of that scale. The five remaining cases, however, showed remarkable consistency.

Each of these patients was sent to the hospital from a medical hospital, with an emergency commitment already approved by the appropriate county office. In all five cases the emergency room staff felt that the patient was no longer acutely dangerous. Typically, these were patients who had been suicidal or violent when intoxicated but who showed no such signs after having been treated at the medical hospital for several days. Patients in similar conditions who came on their own to the emergency room would ordinarily not be committed. Four of these five patients, however, were committed.

Several things may account for these commitments without the legal criteria being met. Certainly one of the potential explanations is that all of these patients were seen as needing some sort of treatment and that clinicians chose to ignore the remaining requirements of the law. Although cited regularly in the literature as a likely explanation for such anomalous cases, this motivation for commitment may not have been the most influential factor at work here. In our discussions of

these situations with the staff, the dominant explanation for pursuing commitment was fear of liability. While the staff understood that they had the right to refuse to accept the commitment, they feared the legal liability of refusing the commitment when it had already been granted by county authorities.

DISCUSSION

We have provided several partial pictures of the adequacy of current procedures for implementing commitment criteria. We have assessed the reliability of ratings regarding committability and looked at the relationships between clinicians' judgments about dangerousness, ability to care for self, and committability. While both the levels of association and the interrelationships of these judgments seem to support contentions that commitment is a consistent and rule-bound process, close analyses of seemingly invalid or significantly unreliable cases reveal two important problems.

First, although there are relatively few such instances, the fact that some patients were seen as committable even though they did not meet the legal criteria for committability is a serious problem. Four such patients were actually committed. In these cases, clinicians acted to enforce a commitment despite their clear opinion that such action was not appropriate. Although one might be encouraged by the fact that this observation indicates a rate of rights' infringement below 1%, the processes underlying these errors of the system still deserve considerable attention and discussion. While it is difficult to assess the direct cause of these decisions, clinicians seemed to feel that—should they have refused to accept the commitment—they might have faced legal liability in the event of a tragedy, or at the least have been seen as blameworthy by their colleagues at the referring facility.

The other issue that limited consensus on committability was the question of how to deal with patients who were willing to admit themselves but who met commitment standards (11). These patients created disagreement between clinicians regarding applicability of the commitment power. One explanation for the disagreement is that the clinicians may have misinterpreted the meaning of the committability ratings in these cases, filling out the scales to reflect the likelihood of commitment actually being pursued in these cases. However, the overall consistency of the rating scales across the great number of other patients seen by this group of clinicians argues against this straightforward explanation. Instead, the inconsistency probably reflects a basic confusion about the applicability of the power to commit.

It is likely that a concern for, but a lack of clarity about, the use of "least restrictive alternatives" is at the root of much of this confusion. Although there is little active enforcement of the statutory right to a least restrictive alternative in the jurisdiction in which this research took place, the notion of securing such a

placement for an individual is still an implicit part of the ethos of the setting. For one group of clinicians, petitioning for involuntary commitment was not permissible if the least restrictive requirement for the patient—that is, voluntary admission—had been achieved. For others, this procedure appeared to be a permissible option as long as minimum statutory requirements were met.

Certainly clinicians have some reason to commit those who are willing to sign themselves in. For one thing, it is a method to ensure that the staff will control the terms of treatment in the hospital. One problem with voluntary admissions is that many patients admit themselves for a few days but leave before any significant therapeutic action can be taken. While this may seem peculiar to those who are accustomed to thinking of a psychiatric hospital as an environment in which to receive treatment, our observations have shown that there are a small number of patients who use a hospital stay for very practical purposes such as safe or timely housing. Involuntary commitment status means that the staff has some control over the possible early termination of a stay.

A second reason for pursuing commitment with voluntary patients is even more pragmatic: the reimbursement structure for those who depended on local public funds for payment of their treatment. In these cases, the hospital staff knew that either the patient had to be committed or the hospital would have to pay the cost of the treatment. In the current fiscal environment, that was a strong impetus to commit these patients.

CONCLUSIONS

Involuntary commitment is a legal institution designed to facilitate psychiatric treatment. As such, it involves a unique power in our society to deprive an individual of liberty. For that reason, it is legally restricted in a variety of ways. Because history has shown that such powers are granted only tenuously, the mental health professions have a major interest in seeing that the power is not abused.

In general, our data seem supportive of the notion that clinicians are fairly consistent in their application of commitment law. By and large, clinicians believe that patients are committable only when they have the characteristics which the law specifies as making them committable. Moreover, clinicians are fairly reliable in their judgments of committability.

However, two features of the commitment process lead to substantial departures from ideal agreement or compliance with statutory assumptions. The first of

these is clinicians' apparent perception that they should not dispute emergency commitments which have been filed by other facilities. The second concerns the commitment of willing patients. The first of these situations appears to promote commitments of a few patients who do not meet the minimum requirements for this action. The second situation appears to prompt disagreement about appropriate use of the power to commit for purposes other than securing immediate treatment for patients.

Fortunately, neither of these problems is irremediable. Legislative or judicial actions clarifying or limiting liability could alleviate much of the tendency to use commitment as a tool of "defensive psychiatry" (12). Other organizational or administrative regulations aimed at clarifying the role of commitment and its relation to the concept of least restrictive alternative could also help alleviate some of the confusion documented by our findings. Finally, modification of reimbursement policies for the indigent would seem to be another appropriate strategy for addressing these issues.

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APPENDIX 1. Form Used for Clinical Ratings of Patient Characteristics

We are interested in obtaining your judgments on a number of dimensions about the patient you just evaluated. Please rate the patient on the following scales:

1. Psychotic	3	2	1	0	1	2	3	Not psychotic
2. Currently suicidal	3	2	1	0	1	2	3	Not suicidal
3. Chronically suicidal	3	2	1	0	1	2	3	Not chronically suicidal
4. Has place to live	3	2	1	0	1	2	3	Lacks place to live
5. Needs immediate treatment	3	2	1	0	1	2	3	Does not need immediate treatment
6. Needs long-term treatment	3	2	1	0	1	2	3	Does not need long-term treatment
7. Currently dangerous to others	3	2	1	0	1	2	3	Not currently dangerous to others
8. Chronically dangerous to others	3	2	1	0	1	2	3	Not chronically dangerous to others
9. Able to care for self	3	2	1	0	1	2	3	Unable to care for self
10. Commitable	3	2	1	0	1	2	3	Not commitable
11. Hostile	3	2	1	0	1	2	3	Not hostile
12. Probably assaultive in a ward environment	3	2	1	0	1	2	3	Probably not assaultive in a ward environment

An Empirical Study of Emergency Commitment

Larry R. Faulkner, M.D., Bentson H. McFarland, M.D., Ph.D.,
and Joseph D. Bloom, M.D.

The authors examine the emergency commitment process in one Oregon county and present data that document the impact of a local detention facility. The study reconfirms the dependence of commitment processes on the mental health system in which they occur, illustrates the relative inability of specific laws to determine the actual nature of commitment processes, provides support for the concept of community care for the people involved, and points to the need for additional research to clarify the effects of commitment procedures.

(Am J Psychiatry 1989; 146:182-186)

Emergency commitment is a provision of most state civil commitment statutes (1, 2). Its stated purpose is usually to provide for the hospitalization of those persons who are believed to meet the criteria for commitment but for whom the regular commitment procedures are not possible or are inappropriate because of the existence of an emergency situation. There have been few empirical studies of the use of emergency commitment procedures. In earlier work we reported that the overall rate of emergency commitment was similar for urban and rural Oregon counties (3), but we also noted wide variability in the rates of individual counties within the urban and rural groups (3, 4). We suggested that some urban counties might be using the emergency commitment procedures inappropriately to bypass the regular commitment process and hypothesized that the use of emergency commitment in any area was closely related to the structure and function of the local mental health system. Miller and Fiddleman (5) found dramatic differences in the rate of emergency commitments between urban and rural counties in North Carolina as well as between those counties which were close to or far from a state hospital. They also suggested that emergency procedures were being

used to achieve ends other than those intended by the statutes.

The main goal of this paper is to examine in detail the emergency commitment process in one Oregon county. The Oregon county under investigation traditionally has had one of the highest rates of emergency commitment in the state. For a circumscribed period during fiscal year 1983-1984, however, this county experienced a precipitous drop and subsequent increase in the number of its emergency commitments. These changes coincided with the opening and closing of a local facility designed to detain people who were involved in the civil commitment process. We begin with a brief overview of Oregon's commitment process, illustrating the role played by emergency commitment procedures. We then describe the modification of the commitment system in the study county from fiscal year 1982-1983 to fiscal year 1984-1985; present data which document the significant changes that occurred; and examine the characteristics of people who were involved in the commitment process in the study county before, during, and after the changes took place. We conclude with a discussion of our results and their programmatic and research implications.

People may enter Oregon's regular civil commitment process at the local level as a result of a petition filed by any two citizens or by an emergency "hold" initiated by a peace officer or a physician. Subsequently, an investigation is conducted by a mental health professional from the local county mental health program. The investigator makes a recommendation to the judge concerning whether or not there is probable cause that the detained person is "mentally ill." Oregon statutes state that a mentally ill person is "a person who, because of a mental disorder, is either (a) dangerous to himself or others; or (b) unable to provide for his basic personal needs and is not receiving such care as is necessary for his health or safety" (6). If the judge believes that probable cause of mental illness exists, the person is scheduled for a commitment hearing. If the judge at the hearing believes that clear and convincing evidence of mental illness exists, the person may be referred to voluntary treatment, placed on conditional release, or committed to the Oregon Mental Health Division for up to 180 days. If committed to the Oregon Mental Health Division, the person may be placed in an Oregon state hospital or referred to a range of other hos-

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pital or nonhospital community programs at the discretion of the division.

In addition to this regular civil commitment process, Oregon statutes provide for an emergency commitment to accommodate those areas of the state where judges are not always available. Under this provision, a person can be committed directly to a state hospital at the request of any two persons with the support of two physicians (or the county health officer) and the agreement of the state hospital that an emergency exists. An emergency commitment may last no longer than 15 days. Within that time, the state hospital superintendent must determine whether the committed person should be converted to voluntary status or released or should have a regular commitment hearing. Functionally, this determination is equivalent to an investigation under the regular commitment process.

METHOD

The methodology employed in the study consisted of three components. First, we examined the structure and function of the civil commitment system in the study county from fiscal year 1981–1982 to fiscal year 1984–1985 and documented the significant changes that occurred during that period. Second, we studied the local county mental health program and the nature of the commitment process in the study county from fiscal year 1981–1982 to fiscal year 1984–1985. Third, we examined county mental health program and state hospital data pertaining to the people involved in the study county's commitment process during the period under investigation in order to determine whether there were any changes in their characteristics.

THE CIVIL COMMITMENT PROCESS IN THE STUDY COUNTY

The study county has the second largest population in Oregon, with a census in excess of 260,000. The civil commitment process in the study county, however, is very atypical when compared to the state as a whole. In fiscal year 1981–1982, the entire state of Oregon had an investigation rate of 15.3 per 10,000 population. Eighteen percent of the investigations consisted of citizen petitions; 47%, peace officer holds; 30%, physician holds; and 5%, emergency commitments. The hearing, commitment, and emergency commitment rates were 6.5, 4.4, and 0.7 per 10,000 population, respectively. In the study county, however, the investigation rate was 7.4 per 10,000 population. Thirty percent of the investigations consisted of citizen petitions; 4%, peace officer holds; 15%, physician holds; and 51%, emergency commitments. The hearing, commitment, and emergency commitment rates were 4.0, 2.6, and 3.8 per 10,000 population, respectively.

After a close review of the commitment system in the study county, we believe that its large numbers of emergency commitments were due to the lack of a suitable local facility in which to detain people who were being considered for civil commitment. The absence of such a facility was the result of a complex series of political and financial factors relating to the local hospital, private psychiatrists, and the local county mental health program. The final result, however, was that the local hospital was not willing to be used as the detention facility for those people who were very disturbed, extremely dangerous, or unable to pay for their care. Peace officer holds could have been placed on most of these people and they could then have been detained at a state hospital about 60 miles away. This procedure would have required that peace officers travel to the state hospital two to three times for each peace officer hold: to take the person there initially, to bring the person back to the study county for the commitment hearing, and then to return those people who were committed. There were no resources in the sheriff's budget to pay for this expense. As a result, peace officers almost always refused to place anyone on a peace officer hold. They would, however, help in the emergency commitment process. The latter entailed merely one trip to the state hospital, since hearings on emergency commitments are held in the county where the state hospital is located. Since emergency commitments did not result in a local investigation or hearing, they also saved the study county's mental health program and court resources.

In the early 1980s, the Oregon Mental Health Division began to encourage county mental health programs to decrease their referrals to state hospitals. State funds were shifted to the county mental health programs contingent upon their ability to keep patients out of the state hospital. This task was very difficult for the study county's mental health program, since local hospital resources were unavailable for most of the patients who were sent to the state hospital. To correct this deficiency in the local service system, county mental health program staff, in cooperation with the sheriff's department, developed a mental health emergency unit, which opened on May 2, 1983. The mental health emergency unit was operated by nonmedical staff from the county mental health program, who were very concerned about protecting patients' rights. A team approach was used to provide treatment, and psychiatric consultants directed the clinical care of the patients. The cost of detention in the mental health emergency unit was approximately \$250.00 per patient day. This figure compares to a conservative estimate of about \$135.00 per patient day at the state hospital during the same time period. Funding for the mental health emergency unit was obtained predominantly from state and county general revenues.

The nature of the civil commitment process in the study county changed dramatically with the opening of

TABLE 1. Effect of Mental Health Emergency Unit on the Civil Commitment Process in an Oregon County^a

Fiscal Year Quarter	Num- ber of Investi- gations	Route to Investigation								Outcome					
		Petition		Peace Officer Hold		Physician Hold		Emergency Commit- ment		Hearing		Commit- ment		Placement in State Hospital	
		N	%	N	%	N	%	N	%	N	%	N	% of Hear- ings	N	% of Commit- ments
1982-1983															
1	49	24	49.0	0	0.0	17	34.7	8	16.3	21	42.9	16	76.2	15	93.8
2	45	13	28.9	1	2.2	11	24.4	20	44.4	23	51.1	20	87.0	18	90.0
3	46	12	26.1	1	2.2	18	39.1	15	32.7	18	39.1	14	77.8	14	100.0
4	55	18	32.7	9	16.4	17	30.9	11	20.0	17	30.9	14	82.4	14	100.0
1983-1984															
1 ^b	51	11	21.6	22	43.1	18	35.3	0	0.0	8	15.7	7	87.5	6	85.7
2	54	15	27.8	6	11.1	27	50.0	6	11.1	6	11.1	5	83.3	5	100.0
3	68	14	20.6	1	1.5	17	25.0	36	52.9	8	11.8	8	100.0	8	100.0
4	58	13	22.4	0	0.0	19	32.8	26	44.8	8	13.8	7	87.5	7	100.0
1984-1985															
1	62	12	19.4	0	0.0	23	37.1	27	43.5	14	22.6	10	71.4	10	100.0

^aSignificant differences between first quarters in petitions ($\chi^2=6.51$, $df=2$, $p<0.05$), peace officer holds ($\chi^2=44.28$, $df=2$, $p<0.0001$), and emergency commitments ($\chi^2=33.06$, $df=2$, $p<0.0001$) but not in physician holds ($\chi^2=1.10$, $df=2$), investigations ($\chi^2=1.88$, $df=2$), hearings ($\chi^2=5.77$, $df=2$), commitments ($\chi^2=3.71$, $df=2$), or placements in state hospital ($\chi^2=3.84$, $df=2$).

^bQuarter in which mental health emergency unit was open for entire quarter (May 2, 1983, to Nov. 23, 1983).

the mental health emergency unit. Peace officers agreed to place people on holds and bring them to the mental health emergency unit for detention and subsequent investigation. The time and travel expense factors that had previously promoted emergency commitments then worked to prevent them, since peace officer holds and local detention avoided the necessity for most trips to the state hospital.

This new civil commitment system was to have a very short life, however, as Oregon's disastrous economy resulted in a large budget deficit in the study county. County administrators refused to support the mental health emergency unit, realizing that they could shift the economic burden back upon the state to provide services for the people involved. No extra funds were available from the Oregon Mental Health Division to replace the lost county revenues. As a result, the mental health emergency unit closed on Nov. 23, 1983, prompting a return to the previous dependency on emergency commitment procedures.

The data presented below document the nature of the study county's civil commitment system and the people who were involved in it before, during, and after the mental health emergency unit was in operation. Several other factors must be considered that could have had an impact on the system as well. There were no significant modifications in the commitment statute and no major population changes in the study county from fiscal year 1982-1983 to fiscal year 1984-1985. In addition, county mental health program staff do not believe that there were major changes in the attitudes or behavior of local physicians, prosecuting and defense attorneys, or judges during the study period.

RESULTS

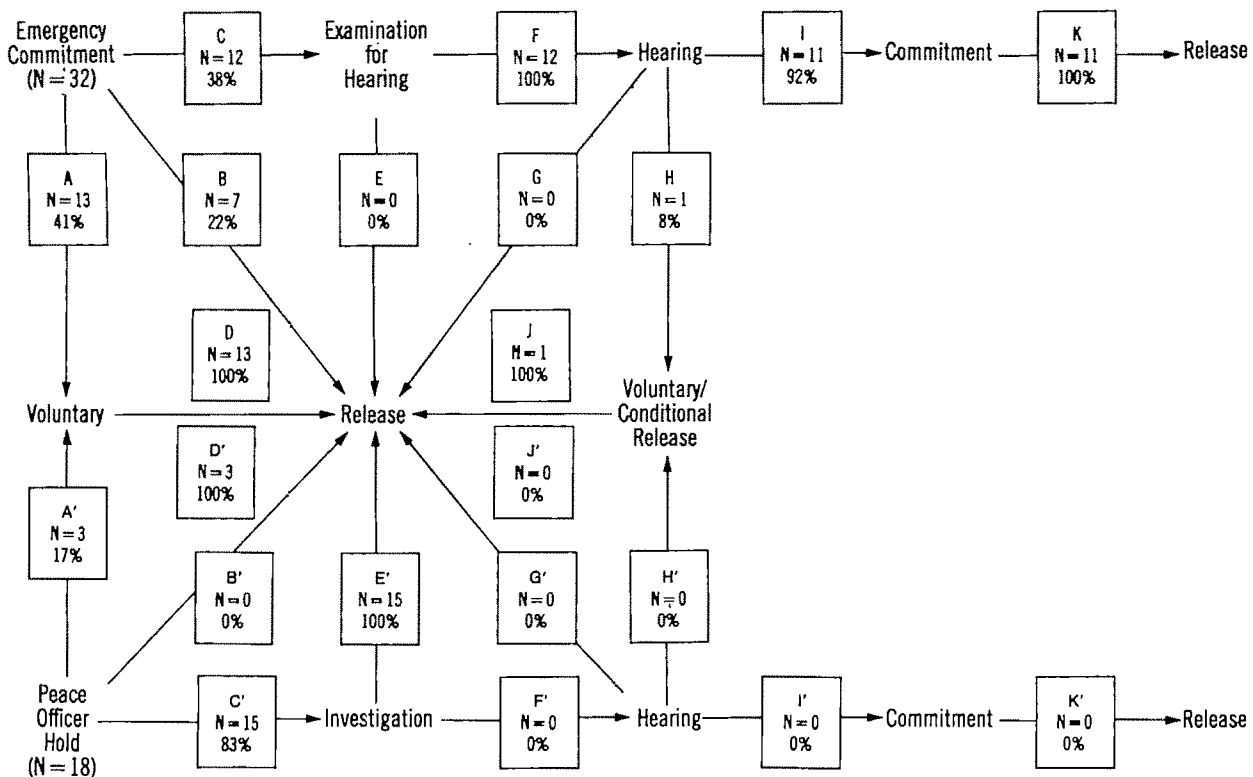
Table 1 provides data pertinent to the civil commitment process in the study county from the first quarter (July 1-Sept. 30) of fiscal year 1982-1983 through the first quarter of fiscal year 1984-1985. Since the mental health emergency unit was in operation from May 2, 1983, until Nov. 23, 1983, the only quarter in which it was entirely open was the first quarter of fiscal year 1983-1984. Therefore, table 1 contains data from 1 year before to 1 year after this quarter.

Emergency commitments are listed in table 1 as one of the routes to an investigation. Technically this definition is not correct, since the state hospital superintendent, rather than an investigator, determines whether people who have undergone emergency commitments should have a commitment hearing. Functionally, however, this determination is very similar to the investigation that takes place for people who are the subjects of citizen petitions, peace officer holds, or physician holds.

A comparison of the data from the first quarters of fiscal years 1982-1983, 1983-1984, and 1984-1985 reveals that very significant changes did indeed occur in the number of peace officer holds and emergency commitments (table 1). The rest of the data remained fairly constant. The change in the numbers of petitions was barely significant and is due to the unusually large number during the first quarter of fiscal year 1982-1983. It appears that the way in which people arrived at the point of an investigation changed dramatically during the first quarter of fiscal year 1983-1984, when there was a shift from emergency commitments to peace officer holds.

To investigate this situation further, we examined

FIGURE 1. Outcomes for People in an Oregon County Who Underwent Emergency Commitment and for Those Placed on Peace Officer Holds and Examined at a Mental Health Emergency Unit^a



^aData for emergency commitment are from the first quarters of fiscal years 1982–1983 and 1984–1985, and those for peace officer holds are from the first quarter of fiscal year 1983–1984. Significant difference between groups in outcomes A, B, C/A', B', and C' ($\chi^2=10.5$, $df=2$, $p<0.01$) and in outcomes E, F/E', and F' (corrected $\chi^2=23.1$, $df=2$, $p<0.0001$).

available county mental health program and state hospital records for those people who were the subject of an emergency commitment during the first quarters of fiscal years 1982–1983 and 1984–1985 or of a peace officer hold during the first quarter of fiscal year 1983–1984. Records were available for 32 (91%) of the 35 people on emergency commitments and 18 (82%) of the 22 on peace officer holds. Since a comparison of the people on emergency holds during the first quarters of fiscal years 1982–1983 and 1984–1985 revealed no significant differences, data pertaining to those groups were combined for comparison with the data concerning people on peace officer holds during the first quarter of fiscal year 1983–1984.

The people in the emergency commitment (N=32) and peace officer hold (N=18) groups were similar in demographic characteristics, diagnoses, treatment and investigation histories, and reasons for investigation. They were typically young men and women who were white, single or divorced, unemployed, and high school graduates and who lived alone or with friends in the study county. About three-quarters of the emergency commitment group and half of the peace officer hold group had a major mental illness (organic mental disorder, mental retardation, schizophrenia, schizoaffective disorder, bipolar disorder, or major depres-

sive disorder). Almost half of both groups had a secondary diagnosis of either substance abuse or personality disorder. In the emergency commitment group, about two-thirds were current patients of the study county's mental health program and about four-fifths had a prior history of psychiatric hospitalization. In the peace officer hold group, one-third were current patients of the study county's mental health program and two-thirds had a prior history of psychiatric hospitalization. On the average, patients in both groups had been investigated about once in the past and about half had a history of an emergency commitment. In both groups, the most frequent reason for investigation was dangerousness to others, followed by dangerousness to self and then grave disability. Corrected chi-square and t tests yielded no significant differences between the emergency commitment and peace officer hold groups on the above comparisons.

Individual case data on the emergency commitment and peace officer hold groups also revealed what happened to people after they entered the civil commitment process in the study county. Figure 1 illustrates the possible outcomes for the two groups and the number and percentage of people in each outcome category. Despite the similarities of the people in the two groups, several significant differences in outcome are

apparent. While only 38% of the people on emergency commitments had an examination to determine whether or not they should have a commitment hearing, a hearing was recommended for all who were examined and 92% of the hearings resulted in a commitment. On the other hand, while 83% of the people on peace officer holds were investigated, hearings were not recommended for any of them and none was committed.

Differences in the average detention times between the two groups are also very apparent. In the emergency commitment group, it required an average of 7.3 days to complete an examination for a hearing, another 4.4 days to conduct a hearing when it was recommended, and 73.2 days to treat and release those people who were committed. In the peace officer hold group, however, it only required an average of 1.8 days to complete an investigation and another 2.3 days to arrange for a person's release. Overall, the average detention time for the emergency commitment group was 45.3 days, compared to 4.4 days for the peace officer hold group ($t=3.14$, $df=48$, $p<0.005$, two-tailed test). Since the costs per patient day in the mental health emergency unit and state hospital were approximately \$250.00 and \$135.00, respectively, the average costs of detention were \$6,115.50 for the emergency commitment group and \$1,100.00 for the peace officer hold group.

DISCUSSION

We believe that there are several important conclusions to be made from our study. First, it confirms our previous work documenting the dependence of civil commitment processes on the structure and function of the mental health system in which they occur (7). The addition of the local mental health emergency unit enabled peace officers to become more involved in commitment procedures and county mental health program staff to focus attention on diversionary strategies that appear to have been very effective. As Miller and Fiddleman found in North Carolina (5), when peace officers in the study county were faced with procedures that were time consuming and costly, it appears that they would just as soon have not been involved in the commitment process at all.

Second, the fact that an urban county could become dependent on a commitment procedure designed for use in rural areas points out the relative inability of specific laws to determine the nature of commitment processes. A law can perhaps set broad limits with respect to who can be committed and the types of procedures that should be employed, but whether or not its intent is followed will depend on the interaction of a complex set of legal, political, economic, social, medical, and many other factors that are still poorly

understood. As we postulated earlier (4), and as Miller and Fiddleman noted in North Carolina (5), it appears that emergency commitment procedures are being used in some areas to achieve ends other than those intended by the statutes. Efforts are currently underway in Oregon to modify the civil commitment statute and eliminate emergency commitments, but it remains to be seen what effect this change will have.

Third, the significant differences in outcomes and average detention times and costs between the emergency commitment and peace officer hold groups provide strong support for the development of local alternatives to state hospital care for people involved in the commitment process. These differences also underscore the necessity for mental health administrators to take a systems approach to the provision of services. While it may have been "penny wise" for the local administrators to close the mental health emergency unit, it appears to have been "pound foolish" in the long run. Any enthusiasm for these results must be tempered by the fact that we do not know whether or not local care in the mental health emergency unit was more effective than care provided in the state hospital. We are currently conducting a follow-up study of the emergency commitment and peace officer hold groups in an attempt to answer this question.

Finally, this study suggests the need for additional research. We need more analyses of the manner in which commitment processes take place at the local level in order to understand the dynamic relationship that exists among the mental health, criminal justice, and civil commitment systems. Even more importantly, we need studies of the natural history of people involved in civil commitment. Global data can provide a broad overview of civil commitment, but it requires individual case data to understand what happens to people as they enter and leave the process and to determine whether or not commitment procedures have a significant impact upon their lives.

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Civil Commitment Standards and Patient Mix in England/Wales, Italy, and the United States

Steven P. Segal, Ph.D.

Although England/Wales, Italy, and the United States share a common policy of deinstitutionalization, their mental health systems differ considerably. Each country's civil commitment standards define patient eligibility criteria along one of two primary dimensions—need for treatment or degree of dangerousness. These differential selection criteria result in mental health systems serving different subgroups of the total population. The criteria in England/Wales target older women; in the United States, younger men; and in Italy, a group balanced in age and sex. Implications for the current debate on civil commitment policies are considered.

(Am J Psychiatry 1989; 146:187–193)

Although England/Wales, Italy, and the United States share a common policy of deinstitutionalization their mental health systems differ considerably with regard to patient selection and resulting patient mix. Differences appear to derive from prevailing civil commitment standards—the rules governing involuntary detention.

Civil commitment standards in each country are defined by one of two types of eligibility criteria—either need for treatment or degree of dangerousness. Implementing civil commitment standards involves varying degrees of practitioner judgment in admission decision making. Constraints on professional discretion in civil commitment decision making derive from three sources: 1) the breadth of the standard, i.e., the number of different types of people covered by the stan-

dard; 2) the precision of the standard—the degree of specificity associated with the standard; and 3) administrative or judicial review of the admission procedure. In this paper, consideration of professional discretion relates primarily to the breadth and the precision of the standard rather than procedural review. This study will show how broader discretionary powers associated with the greater breadth and the lack of precision in the need-for-treatment standard, as opposed to the restricted population focus (breadth) and increased precision of the dangerousness standard, have led to very different patient groups in each country. Further, the study will demonstrate that the choice of civil commitment standards reflects the basic social philosophy in each country.

CIVIL COMMITMENT CRITERIA AND PROFESSIONAL DISCRETION IN PATIENT SELECTION

The 1930 Mental Health Act in England/Wales created a system of civil commitment based on the delegation of discretion to the psychiatric profession to determine who was in need of treatment. The Mental Health Act was a move away from the precise “legalistic” criteria of the 1890 law, to an orientation that has prevailed in Britain through revisions in 1954 (1) and 1983. The standard for involuntary detention became “suffering from a mental disorder that would require containment for reasons of health and safety” (2), where the mental health professional defines these circumstances and can choose to serve those individuals the professional believes fall within his or her “direct practice competence.” The Mental Health Act is purposefully vague; it lacks precision.

During the past 25 years, a majority of states in the United States have changed involuntary admission criteria from “in need of treatment due to mental disorder” to “being a danger to oneself or others due to mental disorder.” This change has shifted the emphasis of admission criteria from broad professional discretion (based upon a purposefully vague and broad standard) to a legally specifiable dangerousness standard (3–5)—one that restricts professional discretion by narrowing the breadth of the standard to focus on a particular subpopulation of the mentally ill.

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This change of standards in the United States reflects the intent of the courts that found traditional need-for-treatment standards unconstitutional by virtue of their breadth and lack of precision. The courts sought in the dangerousness criterion a more stringent standard commensurate with due process rights (6). Limited empirical research in the United States seems to support the observation that psychiatric decision making under the dangerousness criterion is significantly less discretionary than under the need-for-treatment criterion. While one report indicates that 94% of patients involuntarily admitted to two hospitals under the dangerousness criterion displayed behavior conforming to the standard (7), two comparable studies found that only 31% and 36%, respectively, of the patients involuntarily admitted to the hospital under a need-for-treatment criterion actually met the statutory description (8). Thus, in the United States, mental health professionals operating under the dangerousness standard seem more constrained to accept those who meet the standard. British professionals, in contrast, can exercise more selectivity as to whom they serve.

PATIENT MIX

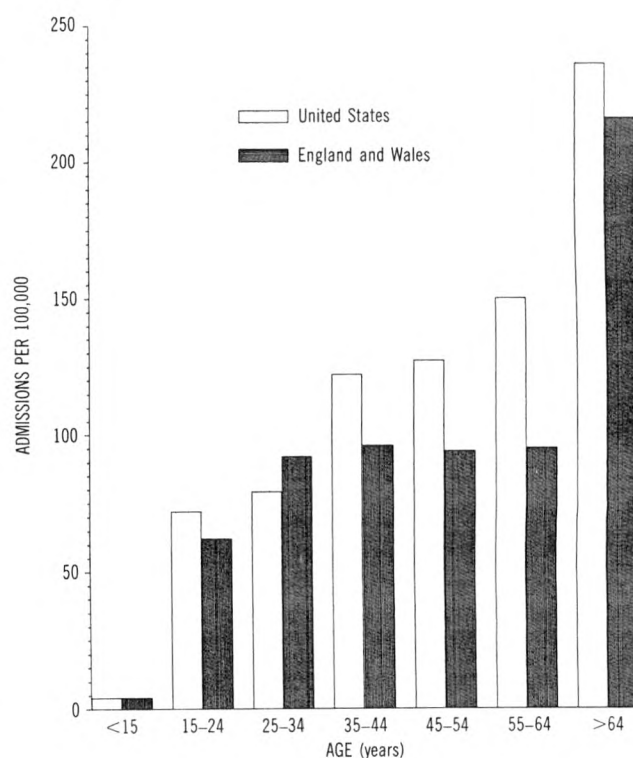
A comparison of age and gender distribution rates of first admissions in England/Wales, Italy, and the United States illustrates how the civil commitment standard changes have reshaped the service populations of their respective systems.

Age Distribution Rates and Patient Selection Criteria

Figure 1 shows the age distribution rates of first admissions per 100,000 for the United States and England/Wales in 1955, when both countries employed the need-for-treatment standard (comparable figures are unavailable for Italy) (9; 10, see also same reports for 1949–1951). The systems appear quite similar, with the exception of a greater emphasis in the United States on patients in their middle years. Figure 2 presents the comparable age distribution for 1980—a period following the United States' conversion to a dangerousness standard (11, 12). The British system, compared with that of the United States, places an emphasis on serving an older population. The United States, on the other hand, has completely reoriented its inpatient system over the past 25 years, a period paralleling its shift to the dangerousness standard. It has moved from an emphasis on an age group similar to that served in England/Wales to an emphasis on youth.

In a comparison of the inpatient first admission graphs in figure 2, it is apparent that the function of inpatient care in the United States and in England/Wales is very different. The decrease in the mentally ill aged in the U.S. mental health system can be attributed to their reclassification and relocation among the frail elderly in nursing home care. However, the replacement of the elderly in mental hospitals by those in the

FIGURE 1. Age Distribution of First Admissions to State and County Mental Health Facilities in the United States and England/Wales, 1955^a



^aU.S. data from Kramer (9), data on England and Wales from British Registrar General (10).

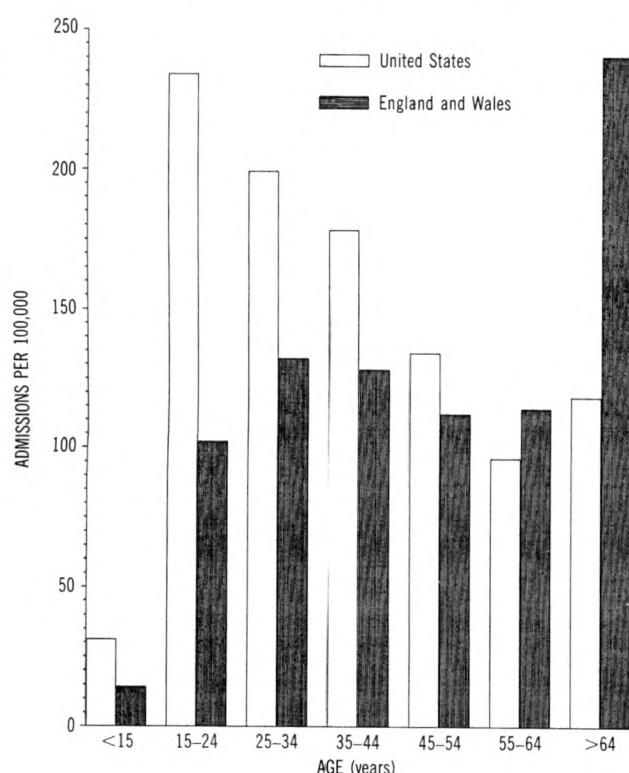
15- to 24-year-old age group indicates that the current interpersonal environment of inpatient settings, as well as the types of disorders dealt with in the United States and England/Wales, are approaching opposite poles.

The increase in young patients in the United States appears to reflect the dangerousness criterion in that 1) the prevalence of behavior considered dangerous to others is highest in the 15- to 24-year-old group and is lowest in the 45 and older age groups (13), and 2) the prevalence of adolescent suicide and suicide attempts has been increasing at an alarming rate (14).

As in the United States, the prevalence of violent crime in England/Wales is at its height in the 14- to 21-year age group; since 1975 there has also been an increase in the prevalence of violence (15), adolescent suicide, and suicide attempts (16) in England/Wales. However, the prevalence of actual suicides and violent crime in England/Wales is *much* lower than in the United States. A conservative estimate of the U.S. suicide rate in 1980 for the 15- to 24-year age group was 12.3 per 100,000 (17); in England/Wales, the comparatively conservative 1982 rate was approximately 6.68—i.e., nearly half the U.S. rate (computed from Home Office statistics [18] and adjusted according to Office of Health Economics procedures [16]).

While British rates of suicide and violent crime are lower than U.S. rates for the 15- to 24-year age group,

FIGURE 2. Age Distribution of First Admissions to All Inpatient Facilities in the United States and England/Wales, 1980^a



^aU.S. data from NIMH (11), data on England and Wales from British Department of Health and Social Security (12).

suicide attempts occur with more equal frequency in the two countries (19, 20). There are large numbers of individuals who have attempted suicide and many troubled adolescents receiving services in general hospitals in England/Wales who are not receiving psychiatric help and who therefore are not represented in psychiatric inpatient first admission rates (16, 21–23). Until recently suicide attempts, especially deliberate self-poisoning, have been considered by British psychiatry to be a social problem outside of direct practice competence. In the United States, however, it is precisely this group of patients that commands a major segment of services offered by the mental health care system (14).

Differences in the patient composition of the U.S. and British systems also derive from the proviso in the British Mental Health Act that individuals with psychopathic diagnoses need not be taken unless they are “amenable to treatment.” To the extent that antisocial behavior is used as an indicator of psychopathic disorder, many patients with troublesome profiles may be excluded from the British mental health service at professional discretion. Because antisocial behavior occurs most frequently in the 15- to 34-year age groups, this proviso may partially explain the smaller representation of 15- to 24-year-old patients in the British system.

It would appear that the differences in patient mix between the two countries are a function of the fact that Britain’s civil commitment standard—the need-for-treatment standard—allows for selection of patients on the basis of professional preferences, while the U.S. standard provides more specific guidelines for patient selection. In the former case, the standard controls the patient mix by default to professional discretion; in the latter, by specification.

Gender and Patient Selection Criteria

The importance of professional discretion in the traditional need-for-treatment standard and its restriction in a system structured by the dangerousness criterion are further evidenced by changes in the Italian system. In 1968, as part of law 431, the “Mariotti reform,” Italy allowed its first voluntary admissions to mental hospitals; in 1978 the country eliminated the dangerousness criterion, making compulsory admissions contingent on a finding that care and rehabilitation were necessary and urgently needed (24). The consequence we should expect—given that only a small proportion of women engage in dangerous behavior at any age—is that new admissions to mental hospitals in Italy would change from a group consisting primarily of men to a more evenly balanced group or, as in the English system, a group with more women. Further, the direction of this change should be exactly the opposite of that in the U.S. system, which moved from a need-for-treatment criterion to the dangerousness criterion. Indeed, Pastore et al., in attempting to understand the new Italian service system, observed that a major difference between old and new cases is a greater predominance of women among new cases as opposed to the predominance of men in the past (D.V. Pastore, M. Marsili, A. Debernardi, unpublished paper, 1984). Torre and Marinoni (25) also noted that admission rates in Italy decreased after passage of law 180 but to a greater extent among men than women.

Table 1 compares the limited number of empirical studies available (26–29) on first admissions in northern Italy with gender distribution rates of first admissions in the United States and England/Wales in the years covered by these studies. (No Italian national statistics on gender or age distribution rates of first admissions are available.) The stability of the English rates, compared to changes indicating a more pronounced emphasis on males in the United States and a change in the opposite direction in the Italian statistics, forms a natural experiment offering some confirmation of the import of civil commitment standards and the degree of professional discretion they embody in determining patient mix. Clearly, systems molded by the dangerousness criterion have a higher proportion of male patients, while the need-for-treatment criterion brings more women into the system.

TABLE 1. Gender Distribution of First Admissions to Psychiatric Inpatient Facilities in the United States, England and Wales, and Northern Italy, 1946–1985

Period	Percent of First Admissions					
	United States ^a		England and Wales ^b		Northern Italy ^c	
	Men	Women	Men	Women	Men	Women
1946–1947	52	48				
1948–1949						
1950–1951			42	58		
1952–1953						
1954–1955	56	44	42	58		
1956–1957						
1958–1959						
1960–1961	56	44				
1962–1963						
1964–1965						
1966–1967						
1968–1969	60	40				
1970–1971						
1972–1973	68	32	41	59	62	38
1974–1975	67	33	41	59		
1976–1977					51	49
1978–1979						
1980–1981	68	32	43	57	52	48
1982–1983					54	46
1984–1985					43	58

^aFirst admissions to state and county mental hospitals, 1946–1947, 1954–1955, 1960–1961, and 1972 (9); first admissions to all psychiatric hospitals, 1974–1975 and 1980–1981 (11).

^bFirst admissions to all psychiatric hospitals in England and Wales, 1950–1951 and 1954–1955 (10) and 1972–1973, 1974–1975, and 1980–1981 (12).

^cFirst admissions to all types of psychiatric facilities as estimated by five studies conducted in Mantova in 1968–1976 (N=86) (table reports average for 1968–1976) (26), Trieste in 1977 (N=226) and 1984 (N=161) (27), Cagliari in 1981 (N=372) (28), and 36 facilities in northern Italy in 1983 (N=209) (29).

INTERPRETING CROSS-NATIONAL DATA: ADDITIONAL EVIDENCE

While the standard influences patient mix, it only sets broad boundaries that are modified by administrative and organizational preferences. Its full impact is experienced over many years. Given the difficulty of interpreting cross-national trends and the slow process by which the law effects change, two additional sources of evidence adding credence to my interpretation of the international age and sex variations should be considered.

Secular Trends in the Reporting of Dangerousness Among the Mentally Ill

In the United States before the early 1960s, in the need-for-treatment era, studies of criminal activity by former psychiatric patients, with the general population used as a control, showed that patients had an equivalent amount or somewhat less criminal involvement than the general population. In the late 1960s and early 1970s, when changes in civil commitment

standards were occurring, studies showed that criminal involvement by former patients began to exceed that of the general population. Finally, in the late 1970s, with the broad implementation of the dangerousness standard in civil commitment, studies showed that former patients' rates of criminal involvement were higher than those of the general population. Rabkin (30) concluded that these observed rate differentials were due to the admission of a greater proportion of mental hospital patients in the late 1970s who had criminal records before their hospitalization and continued their criminal involvements after their release. It would thus appear that the dangerousness criterion is effectively being used to select "dangerous" people into the system.

Further support for the observation that patient selection by civil commitment standards tends to account for crime rate differentials between the general and patient populations may be obtained from Gunn's observation (31) of this phenomenon in Britain. On the basis of evaluation of general population crime rates and the number of patients admitted to a psychiatric hospital for a criminal offense, he argued that the crime rates probably do not differ in these two groups. This observation would be consistent with expectations for a system that uses a need-for-treatment standard and corresponds to the results of the U.S. studies conducted in the need-for-treatment era.

Broadening of Civil Commitment Standards in Washington State

In 1979 Washington State became one of the first states to reverse the national trend toward more restrictive admissions criteria by broadening its civil commitment law, moving from a clearly defined dangerousness standard to one allowing for a need-for-treatment criterion. In 1980—the year in which the broadened standard came into effect—as compared with 1976 and 1977 (years preceding the change), there was a large increase in the number of total admissions to Washington state and county hospitals. This, however, was accompanied by a drop of almost 5% in the *proportion* of adult admissions in the 18- to 24-year-old age group—the population at high risk for dangerousness ($Z=5.04$, $p<0.01$, in a comparison of both 1976 to 1980 and 1977 to 1980) (32). (Additions include admissions, readmissions, and returns from extended leave during the reporting year; age distribution of first admission and admission statistics are not available.) Thus, the implementation of a need-for-treatment criterion appears, even in the first year of activity, to have resulted in a reduction in the relative size of the young adult age group. These changes and the observed secular trends in the reporting of dangerousness seem to validate the interpretation of the international age and sex variations in first admissions presented earlier.

THE CONTEXT OF COMMITMENT LAW CHANGES

During the past 5 years a new and increasingly polarized debate has developed in the United States between the advocates of "holding the line" on the dangerousness standard and the advocates of a return to a need-for-treatment standard. The former group views a return to the need-for-treatment standard as abandonment of the civil rights orientation embodied in the restricted range of decision making imposed by the dangerousness standard. The latter group views the dangerousness standard as inappropriately forcing professionals to treat untreatable patients and forcing them to abandon their commitment to a paternalistic approach to patients (33). The data presented here show that the adoption of either standard represents a preselection of the type of patients who will receive treatment and an altering of the patient mix in the system. With only rudimentary knowledge of how this process occurs, there are at least four factors to consider in understanding such system changes.

Resource Availability

The Washington State results, in contrast to the international data, illustrate how resource availability interacts with civil commitment standards to reshape patient mix. The international data are reported in the context of an effort to reduce utilization of inpatient beds. With declining resources, the civil commitment standard will screen people in a way that results in a system numerically dominated by the selected population. By contrast, the denial of hospitalization to a patient who subsequently murdered two prominent citizens led to a willingness in Washington State to expand inpatient resources. With increasing availability of beds, the civil commitment standard screen will decrease the proportion of ineligible or less desirable groups, although the numbers of individuals in both groups may increase. The standard operates as a means of selective recruitment or outreach.

Restricting Discretion in the Need-for-Treatment Standard

Because the traditional need-for-treatment standard involves the granting of broad discretionary powers to clinical decision makers (6), patient mix could become a reflection of practitioners' service preferences. Recognizing this and being skeptical with regard to the use of unrestricted discretion by clinicians, advocates of a return to a paternalistic need-for-treatment standard have attempted to operationalize the model's selection criteria. Their approach, the Stone-Roth model, sets forth five commitment criteria believed to appropriately limit the discretionary powers of the evaluator (33). Since this model has received only simulated testing with patients currently entering the system, and since these simulations have produced different conclusions about the effect of these limits on discretion-

ary admissions, it is difficult to say how this model would influence patient mix (33; S.K. Hoge, G. Sachs, P.S. Appelbaum et al., unpublished data, 1987). Hoge et al.'s simulation (unpublished) indicates, however, that those patients most likely to be excluded from the system in a shift to the Stone-Roth criteria would be those presenting as a danger to themselves and those who have personality disorders—both are groups likely to come from the 18- to 24-year-old men and suicide attempters discussed earlier. It would seem, therefore, that the Stone-Roth criteria reflect the preferences in case mix embodied in the more traditional need-for-treatment standard.

Shaping the Gatekeepers

The civil commitment standard is important in selecting patients at the time of evaluation, i.e., in immediately bringing a change to the patient mix within the facility. The implementation of the standard, however, also sends a message to gatekeepers as to the characteristics of patients who are to be selectively removed from the system. This is especially true in public emergency rooms where police officers are a major source of referrals and are very much attuned to the types of people admitted and released. Decisions of emergency room evaluators have a direct impact upon the work schedule of the beat officers. A beat officer wishing to take a patient to the hospital for evaluation must get someone to cover the beat. The officer must transport the patient—often a round trip of an hour or two—to a psychiatric emergency facility. After having transported a patient who is subsequently turned away, the beat officer becomes very reluctant to continue to transport such patients for evaluation. This process accelerates the change in patient mix attributable to the standard's selection biases. In effect, the gatekeepers are shaped, in the behavioral sense of the term, to bring in the "appropriate" patients, those patients who will meet the criteria.

Needs-Oriented Versus Rights-Oriented Systems

Culturally, Britain's need-for-treatment standard is consistent with paternalistic social philosophies prevalent in the welfare state. Similarly, Italy's move to a paternalistic standard reflects the increasing power of Western European Communism in Italian thinking. Both of these systems lead very easily to a needs-orientation as compared to the "rugged individualism" embodied in U.S. thought—an individualism reflected in rights-oriented programs.

In a consideration of the rights versus needs theme in patient selection, the analogy may be drawn to the value systems of law and medicine, respectively. The legal rights orientation emphasizes the uniqueness of each individual, regardless of worthiness, and advocates equal protection under the law as well as equal access to care. Following this theme, the "patient," or sometimes "client," is more active in determining the

nature of the help he or she will receive and accept—with the exception of those situations in which the patient's behavior poses a direct threat to self or the community. In the latter situation the law requires the mental health professional to take action. Thus, in a rights-oriented system, the civil commitment standard constrains professional discretion. In fact, with limited resources and a cultural emphasis on individual responsibility, the U.S. system has become a residual service dealing only with the most difficult people.

The British system, viewed in terms of the medical concept of triage, selects those who not only are in need (as determined by professional evaluation), but who can also benefit most from the limited help available and adapt to existing long-term care facilities without the type of disruption experienced by the U.S. services. This kind of system prevailed in the United States during the 1950s but has bowed to the rights orientation because of the direct challenge to the concept of treatment effectiveness. As former U.S. Supreme Court Chief Justice Warren Burger said:

Given the present state of medical knowledge regarding abnormal behavior and its treatment, few things could be more fraught with peril than to irrevocably condition a State's power to protect the mentally ill upon the providing of "such treatment as will give [them] a realistic opportunity to be cured." Nor can I accept the theory that a State may lawfully confine an individual thought to need treatment and justify that deprivation of liberty solely by providing some treatment. Our concepts of due process do not tolerate such a "tradeoff." (34)

Under these circumstances the triage notion breaks down, and the primary arguments for a need-for-treatment criterion allowing for the focus on serving middle-aged and older female patients who are less socially disruptive are: 1) their greater worthiness, 2) their willingness to acquiesce in system norms and cooperate with system procedures, and 3) the fact that other eligible groups are more adequately attended to by other social institutions or are not apparent in the society because of different cultural perspectives.

CONCLUSIONS

Given the limited availability of mental health services and the large pool of people who might qualify for such services, no current national mental health system appears to accommodate all potential users of inpatient care. Analysis of the data available regarding the operation of the civil commitment criteria in England/Wales, Italy, and the United States indicates that it is necessary to understand the health and social services systems of a country as well as its cultural context in order to comprehend the full impact of civil commitment criteria on patient mix. Regardless of this context, however, the substance of the criteria has a clear and specifiable impact on the demographic characteristics of the patient population.

Patient mix or group composition affects treatment strategies, service outcomes, and the social context of inpatient facilities. The mental health system's lack of responsiveness to the young adult chronic patient was partially a lack of recognition of a change in patient mix. Thus, advocating the choice of a civil commitment standard in the current debate is potentially choosing who will be served, how to serve them, and the types of outcomes and work environments evidenced in inpatient facilities.

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The UCLA-University of Utah Epidemiologic Survey of Autism: Prevalence

Edward R. Ritvo, M.D., B.J. Freeman, Ph.D., Carmen Pingree, M.S.,
Anne Mason-Brothers, Lynn Jorde, Ph.D., William R. Jenson, Ph.D.,
William M. McMahon, M.D., P. Brent Petersen, M.D., Amy Mo, and Anne Ritvo

The authors conducted an epidemiologic survey in Utah using a four-level ascertainment system, blind current diagnostic assessments, and DSM-III criteria. Of 483 individuals ascertained, 241 were diagnosed as having autism. The best estimate for the prevalence rate was 4 per 10,000 population. Autism was not associated with parental education, occupation, racial origin, or religion. Sixty-six percent of the autistic subjects scored below 70 on standardized IQ tests, and females scored proportionately lower than males. Twenty (9.7%) of 207 families had more than one autistic sibling, which supports the authors' previous finding that there may be a familial subtype of autism. (Am J Psychiatry 1989; 146:194-199)

Previous epidemiologic surveys conducted in Europe, Asia, and North America (1-13; unpublished 1970 paper of B.H. Brask) estimated the prevalence of autism to be between 2 and 21 per 10,000 in the general population (see table 1—after Ornitz [14]). Three recent critical reviews (14-16) noted that this wide range is most likely due to different methods of ascertainment, lack of pathognomonic symptoms and

signs indicative of autism, use of different diagnostic criteria, and sampling and statistical problems inherent in studying this rare disease in the relatively small populations surveyed.

We designed the present survey to mitigate these problems as much as possible by using multilevel ascertainment procedures, multiple blind diagnosticians, and DSM-III criteria and by surveying the relatively stable, highly cooperative, and geographically accessible population of the state of Utah. We undertook this arduous project because a highly accurate survey is needed to test various hypotheses concerning the etiology and nature of autism (17) and to assist in planning for the lifelong care of our autistic patients.

METHOD

Utah was selected because the population is small enough to survey accurately (1,461,037 according to a 1980 census [18]) yet large enough to yield a projected number of probands to represent the entire spectrum of the disease. The geography of Utah makes the population easily accessible because the vast majority of people (approximately 80%) live along a north-south valley corridor 80 miles long and 17 miles across at its widest point. Health, education, and welfare facilities are highly concentrated: there is one pediatric hospital, one state hospital for the retarded and developmentally delayed, one state hospital for the mentally ill, one prison, one medical school with a pediatric ward and genetic screening service, 51 group homes (including two specifically for autistic children), 10 social service facilities for out-of-home placements, 21 early childhood intervention centers, two schools specifically for autistic pupils, and 11 classrooms for autistic pupils in other schools. There is also a high level of

Received April 19, 1988; revision received July 13, 1988; accepted August 10, 1988. From the Division of Mental Retardation and Child Psychiatry, University of California School of Medicine, Los Angeles, and the University of Utah, Salt Lake City. Address reprint requests to Dr. Ritvo, Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

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TABLE 1. Results of Earlier Prevalence Studies of Autism

Investigator	Year	Area	Age Range (years)	Size of Population	Prevalence per 10,000 Population
Lotter (1)	1966	Middlesex, England	8-10	78,000	7.8
Brask (unpublished)	1970	Aarhus, Denmark	2-14	46,000	4.3
Treffert (2)	1970	Wisconsin, United States	3-12	899,750	3.1
Wing et al. (3)	1976	Camberwell, England	5-14	25,000	8.0
Wing and Gould (4)	1979	Camberwell, England	0-15	35,000	21.2
Hoshino et al. (5)	1982	Fukushima, Japan	0-18	609,848	2.3
			5-11	217,626	5.0
Bohman et al. (6)	1983	Västerbotten, Sweden	0-20	69,000	5.6
Ishii and Takahashi (7)	1983	Toyota, Japan	6-12	34,987	16.0
Gillberg (8)	1984	Göteborg, Sweden	4-18	128,584	3.9
Sugiyama and Abe (9) ^a	1986	Nagoya, Japan	1.5-3	12,263	21.2
Steinhausen et al. (10)	1986	West Berlin, Germany	0-15	279,616	1.9
Matsuishi et al. (11) ^a	1987	Kurume, Japan	4-12	32,834	15.5
Steffenburg and Gillberg (12) ^a	1986	Göteborg and Bohuslän, Sweden	0-10	78,413	6.6
McCarthy et al. (13) ^b	1984	Ireland	8-10	65,000	4.3

^aUsed DSM-III criteria.^bUsed criteria similar to DSM-III.

public awareness and cooperation in matters of health and education throughout the state.

Seventy percent of the population of Utah belong to the Church of Jesus Christ of Latter Day Saints (the Mormon Church) (18), most of whose founders settled in Utah in the mid- to late-nineteenth century. Initially some pioneers practiced polygamy, but this has been against state and church laws since 1890. Genetic research shows no excessive inbreeding or consanguinity (19) and that the gene pool is fully representative of North American and European Caucasian populations (20). The Mormon Church asks members to keep five-generation genealogy records, which, in many cases, were voluntarily made available to us. Income in Utah is mainly derived from mining, manufacturing, farming, and general commerce. In 1982 the fertility rate was 116 births per 1,000 women aged 14-44, one of the highest in the United States (the national rate was 69 births per 1,000 women aged 14-44) (18). This is due to the fact that Mormon Church members traditionally have large families.

Ascertainment Procedures

Vital to the success of the survey was a broad base of community support. A four-level system was used to ascertain possibly autistic persons less than 25 years of age.

Level 1: persons identified as having autism before the survey. One of us (C.P.) conducted a master's thesis case finding project in 1982, lobbied the state legislature to establish a school in Salt Lake City for autistic pupils (the Children's Behavior Therapy Unit) and two group homes for autistic children, and helped to establish the Utah Society for Autistic Children, a chapter of the Autism Society of America, a parent advocacy group. Her contacts through this network of parents, clinicians, and providers of social services and

education formed the basis for this level of case finding.

Level 2: voluntary referrals. Families with possibly developmentally delayed and/or autistic children were solicited through media campaigns. Dozens of newspaper and magazine articles, television and radio broadcasts, and public lectures saturated the state with information about and descriptions of developmental disabilities and autism and requests for voluntary referrals for our free diagnostic services. Ongoing publicity was maintained throughout the entire 4 years of the survey and provided a continuing high level of public awareness and inflow of new referrals.

Level 3: solicited referrals. Referrals were obtained from practitioners, clinics, schools, and social service agencies. Contacts were made at clinics and agencies serving individuals with retardation, developmental disabilities, and autism. These included the State Training School at American Fork, the State Mental Hospital at Provo, the Children's Behavior Therapy Unit in Salt Lake City, the Autism Elementary Group Home, the Autism Adolescent Teaching Home, the Residential Autism Program in Ogden, the Utah Department of Social Services, the Mormon Church Social Services Administration, Youth in Custody, the Special Education Consortium, and special education facilities. Materials describing developmental disabilities and autism and questionnaires with return envelopes were distributed in these facilities to be given to parents. Social service assessment teams reviewed all residential clients in on-site visits for possible referrals to the project. In addition, directors and teachers of autism programs and directors of special education in all 40 school districts in Utah were contacted at least twice during the study. They identified autistic subjects, contacted families, and obtained permission for the research team to contact them directly. All private practitioners who dealt with developmental disabilities

TABLE 2. Sources for Ascertainment of Families With Autistic Subjects in Utah Survey

Source	Families With Subjects Diagnosed Autistic (N=215)		Families With Subjects Diagnosed Not Autistic (N=125)		Families With Subjects Not Diagnosed (N=105)		Total Families Ascertained (N=445)	
	N	%	N	%	N	%	N	%
Level 1: previous survey	90	41.9	18	14.4	29	27.6	137	30.8
Level 2: voluntary referrals—responses to media, lectures	24	11.2	16	12.8	8	7.6	48	10.8
Level 3: solicited referrals								
Autism treatment centers	20	9.3	6	4.8	5	4.8	31	7.0
Educational facilities	14	6.5	15	12.0	5	4.8	34	7.6
Autism society	15	7.0	7	5.6	7	6.7	29	6.5
Parent referrals	7	3.3	21	16.8	4	3.8	32	7.2
Personal contacts	5	2.3	8	6.4	10	9.5	23	5.2
Social service facilities	13	6.0	10	8.0	12	11.4	35	7.9
Physicians, psychologists	11	5.1	2	1.6	0	0.0	13	2.9
Mormon Church	9	4.2	1	0.8	0	0.0	10	2.2
Level 4: case finding—hospitals and residential facilities	7	3.3	21	16.8	25	23.8	53	11.9

were contacted through professional newsletters and publications, notified of the survey, and invited to lectures. Target professionals included psychologists, psychiatrists, child psychiatrists, neurologists, pediatric neurologists, pediatricians, developmental specialists, speech and language therapists, and genetic counselors. Professional conferences were also held at an annual meeting of the Intermountain Pediatric Society and at Grand Rounds at the Primary Children's Medical Center and University Hospital.

Level 4: case finding in the field. Members of the research staff (C.P., E.R.R., and A.R.) screened records in residential facilities, group homes, and state hospitals for the retarded and mentally ill, without reference to patients' or students' names, and identified possible cases of developmental disabilities and autism. To assure confidentiality, appropriate senior staff members of the facilities asked the families of any patient or student so identified for permission to release their names to the research team before we contacted them.

Extensive feedback was provided to all parents regarding our diagnostic opinions and recommendations, including written reports and specific referrals when requested. Public lectures, Autism Society newsletters, and annual progress letters provided information on the progress of the survey and general research news. These measures enhanced cooperation, facilitated case finding as families sought to take advantage of free services, and helped parents and professionals in their ongoing efforts to obtain high-quality services throughout the state.

Diagnoses

DSM-III criteria were uniformly applied. The criteria for the definition of the syndrome of autism of the National Society for Autistic Children (21) are identical to those of *DSM-III* and, for those interested, provide a more detailed description of the symptoms and

TABLE 3. Status of Ascertained Subjects in Utah Autism Survey

Status	Individuals (N=489)		Families (N=445)	
	N	%	N	%
Diagnosed autistic	241	49.3	215	48.3
Diagnosed not autistic	138	28.2	125	28.1
Excluded from study	110	22.5	105	23.6
Moved out of state,				
lost contact	33	6.7	33	7.4
Noncooperative	30	6.1	30	6.7
Older than 25 years	47	9.6	42	9.4

developmental delays pathognomonic of autism. During the course of the survey, in 1985, *DSM-III-R* was published. Since this revised definition was not based on new scientific data and purportedly selects almost identical cases, we did not adopt it or attempt to apply it retrospectively.

For our database, parental consent for release of information was obtained and the following information assembled on each person ascertained: 1) a five-generation family pedigree chart, 2) a checklist of diseases in all first-, second-, and third-degree relatives, 3) a detailed family medical history of first-degree relatives, 4) a 500-item developmental inventory (22), 5) obstetrical records, 6) birth records, 7) postnatal and all subsequent medical records, 8) psychological evaluations, 9) educational records, and, if applicable, 10) vocational records and 11) residential and foster home records.

For the initial screening, independent blind record reviews were conducted by two of us (E.R.R. and B.J.F.) at the University of California, Los Angeles. Each patient was scored on historical and present symptom forms that were developed for this study by modifying the Behavior Observation Scale for Autism (23) and the Ritvo-Freeman Real Life Rating Scale (24) (these forms are available on request). Individuals who

TABLE 4. Prevalence of Autism Among Individuals Born in Utah During 1960–1984

Birth Years	Age Range (years)	All Utah Births	Autistic Subjects ^a	Prevalence per 10,000
1980–1984	3–7	202,336	44	2.17
1975–1979	8–12	184,822	66	3.57
1970–1974	13–17	139,356	44	3.16
1965–1969	18–22	115,235	25	2.17
1960–1964	23–27 ^b	127,871	11	0.86

^a190 autistic subjects born in Utah, plus 49 not born in Utah, plus two autistic siblings older than 25 years equals the total 241 autistic subjects diagnosed.

^bSubjects who were 25 years old at the start of the study were 27 years old by the end of the study.

TABLE 5. Racial Origin and Religion of Families of Autistic Subjects in Utah Survey

Item	Utah Population (%)	Fathers (N=215)		Mothers (N=215)		Families (N=215)	
		N	%	N	%	N	%
Racial origin							
Caucasian	94.66	200	93.0	200	93.0		
Black	0.62	2	0.9	2	0.9		
American Indian	1.32	2	0.9	2	0.9		
Asian	3.41	1	0.5	1	0.5		
Hispanic	4.11	5	2.3	4	1.9		
Arabic	0.0	1	0.5	2	0.9		
Mixed	0.0	3	1.4	3	1.4		
Unknown	0.0	1	0.5	1	0.5		
Religion ^a							
Mormon Church	70.00	—	—	—	—	146	68.2
Other	30.00	—	—	—	—	49	22.9
Mormon Church and other	—	—	—	—	—	19	8.9

^aThe religion of the family of one autistic subject was unknown; percents are based on N=214.

unanimously and unequivocally were determined not to have autism were diagnosed not autistic at this screening. All other individuals were seen in Utah.

For the direct diagnoses in Utah, a team of experienced clinicians from the University of Utah (P.B.P., W.M.M., and W.R.J.) and the University of California, Los Angeles (E.R.R. and B.J.F.), conducted family interviews and current mental status examinations throughout the state on all possibly autistic persons ascertained. Multiple training sessions were held to assure consistent data gathering and coding and application of *DSM-III* criteria. During the interviews all records were reviewed again with the families, a new detailed developmental history was obtained, and a second set of historical and present symptom forms was filled out. The current mental status examination was also coded. Unequivocal cases were diagnosed at this point. Questionable cases were seen again by one or more of the clinicians and a consensus diagnosis was reached at a case conference. When a relative of a proband was suspected of having autism, this individ-

TABLE 6. Educational and Occupational Levels of Parents of Autistic Subjects in Utah Survey

Item	Fathers (N=208) ^a		Mothers (N=208) ^a	
	N	%	N	%
Educational level				
Graduate school completed	36	17.3	16	7.7
College or university graduate	37	17.8	33	15.9
Some college	62	29.8	64	30.8
High school graduate	49	23.6	78	37.5
Some high school (grades 10,11)	16	7.7	12	5.8
Junior high school (grades 7–9)	5	2.4	2	1.0
Currently a student	3	1.4	3	1.4
Occupational level				
Executive or major professional	22	10.6	3	1.4
Manager, proprietor of a medium concern, minor professional	34	16.4	26	12.5
Administrator or semiprofessional	49	23.7	15	7.2
Clerical or sales worker, technician	76	36.7	22	10.6
Semiskilled worker	17	8.2	10	4.8
Unskilled worker	6	2.9	4	1.9
Homemaker	0	0.0	125	60.1
Currently a student	3	1.4	3	1.4

^aThe educational level of seven fathers and mothers was unknown. The occupational level of eight fathers and seven mothers was unknown. Percents for father's occupational level are based on N=207.

TABLE 7. Birth Order of Male and Female Autistic Subjects in Utah Survey

Birth Order	Males (N=186) ^a		Females (N=49) ^b		Families (N=235)	
	N	%	N	%	N	%
First	59	31.7	14	28.6	73	31.1
Second	35	18.8	9	18.4	44	18.7
Third	32	17.2	10	20.4	42	17.9
Fourth	20	10.8	5	10.2	25	10.6
Fifth	17	9.1	4	8.2	21	8.9
Sixth	13	7.0	4	8.2	17	7.2
Seventh	7	3.8	0	0.0	7	3.0
Eighth	1	0.5	3	6.1	4	1.7
Ninth	1	0.5	0	0.0	1	0.4
Twelfth	1	0.5	0	0.0	1	0.4

^aThe birth order of four subjects was unknown: three were adopted and no family information was available for one.

^bThe birth order of two subjects was unknown: they were adopted.

ual was enrolled as a newly ascertained case and underwent the same diagnostic procedures as all others.

An R-Base System V custom database was designed to contain all relevant data. This database is maintained on an IBM XT computer at the University of California, Los Angeles.

RESULTS

Tables 2 and 3 show the sources of the 489 individuals ascertained and their distribution by diagnoses. These figures indicate the success of our strategy to minimize preselection by using broad inclusionary criteria for ascertainment (of 489 persons ascertained

TABLE 8. IQ of Male and Female Autistic Subjects in Utah Survey^a

Item	Males (N=185)		Females (N=50)		Male-to-Female Sex Ratio	Total (N=235)	
	N	%	N	%		N	%
IQ score							
>120	6	3.2	0	0.0		6	2.6
110-119	4	2.2	0	0.0		4	1.7
90-109	15	8.1	3	6.0	5.0:1.0	18	7.7
80-89	21	11.4	3	6.0	7.0:1.0	24	10.2
70-79	23	12.4	5	10.0	4.6:1.0	28	11.9
50-69	46	24.9	13	26.0	3.5:1.0	59	25.1
35-49	42	22.7	10	20.0	4.2:1.0	52	22.1
20-34	24	13.0	12	24.0	2.0:1.0	36	15.3
<20	4	2.2	4	8.0	1.0:1.0	8	3.4
IQ scores grouped by classification of mental retardation							
>70 (no retardation)	69	37.3	11	22.0	6.3:1.0	80	34.0
50-70 (retardation)	46	25.9	13	26.0	3.5:1.0	59	25.1
<50 (retardation)	70	37.8	26	52.0	2.7:1.0	96	40.9

^aThe IQ of five males and one female was unknown.

only 49% were diagnosed autistic). They also indicate that no single source of autistic subjects and no one category for exclusion contained a disproportionate number of subjects, thus minimizing the chances that a particular type of selection bias unduly influenced the results.

The most frequent other related diseases among the autistic subjects were Down's syndrome (three cases), Sanfilippo syndrome (two cases), fragile X syndrome (two cases), Tourette's syndrome (two cases), and Rett's syndrome (four cases). These and other medical data, including an analysis of pre-, peri-, and postnatal factors, are being analyzed separately.

Table 4 shows the prevalence rates of autism found in each of the 5-year age groups. The increase between the 3-7-year-old group and the 8-12-year-old group (2.17 per 10,000 to 3.57 per 10,000) undoubtedly reflects the obvious clinical fact that many patients in the 3-7-year-old group were too young to have shown substantial symptoms and therefore had not been brought for evaluation. Likewise, the steadily decreasing prevalence rates from 13 to 25 years of age reflect the fact that the older patients are more likely to have been misdiagnosed (indeed, the diagnosis of autism was not widely used or codable before publication of *DSM-III* in 1980). Also, many clinicians automatically drop or replace the diagnosis of autism when a patient enters adolescence or adulthood. Our ascertainment procedures were designed to mitigate these problems, and the dropoffs in prevalence would undoubtedly have been greater if not for our special case finding efforts in these older age bands. If we assume that the 8-12-year-old age group is most representative and that we were able to identify only about 90% of all cases in this age group (these assumptions are based on our extensive clinical experience), then the best estimate for the "true" prevalence rate of autism was 4 per 10,000. (The two types of cases we probably under-ascertained, even in the 3-7-year-old age band, were those too mild to have come to clinical attention and

TABLE 9. Families With Multiple Autistic Subjects in Utah Survey

Number of Autistic Siblings in Each Family	Families (N=20)	Subjects		
		Male (N=33)	Female (N=13)	Total (N=46)
Two	17	27	7	34
Two males	12	24	0	24
Two females	2	0	4	4
One male, one female	3	3	3	6
Three	1	2	1	3
Four	1	1	3	4
Five	1	3	2	5

those too severe to allow survival or with such impairment that the symptoms of autism were masked by other evidence of brain damage and/or by profound mental retardation.)

Table 5 shows the distribution of parental racial origin and religion. Table 6 shows the educational and occupational levels of the parents. The distributions of these factors are quite close to those of the Utah population (18). Table 7 shows the distribution of the birth order of the autistic subjects.

Table 8 shows the distribution of IQ by sex and the sex ratios. These results are highly consistent with previous reports (14). Sixty-six percent of the 235 autistic subjects scored in the mentally retarded range (70 or below), and there was a higher proportion of females with very low scores (52% of females and only 38% of males scored less than 50). This difference is also illustrated by the male-to-female ratio of 6.3:1.0 for autistic subjects with IQ scores above 70 and 2.7:1.0 for those with IQs less than 50. (The overall male-to-female sex ratio was 3.7:1.0.)

Twenty families (9.7% of the 207 families of non-adopted, non-fragile-X autistic subjects) had multiple siblings with autism (see table 9). Thirteen of these families were aware that they had more than one autistic child before the survey, three suspected this, and four were identified by the research team. Six of the

families had dizygotic twins. One pair of twins was concordant for autism and of opposite sex. Two sets were nonconcordant and both males. One set included an autistic male and a normal female. One included an autistic male and a female twin who aborted at 4½ months. Finally, one set was an autistic male and a female co-twin who died of herpes encephalitis at 12 days of age.

DISCUSSION

An accurate estimate of the prevalence of autism is necessary if families, health care providers, and educators are to make realistic plans for autistic patients. The result of our survey (our best prevalence estimate is 4 per 10,000) is remarkably close to several previous estimates from around the world (1–13; unpublished 1970 paper of B.H. Brask), which supports its validity.

Our finding that the distribution of autism is not correlated with parental education, occupation, race, or religion confirms our previous survey of California patients (25) and others conducted throughout the world (26, 27). Also, the distribution of IQs and the sex ratios among IQ groups we found are consistent with previous reports (26).

One of the strengths of our survey was the consistent and reliable application of *DSM-III* criteria by experienced clinicians trained to work together. *DSM-III* was adopted in 1980 not only by APA but also by the American Medical Association. We strongly believe it should be used by all clinicians and researchers until new scientific data warrant its modification, improvement, or replacement.

The observation that 20 families (9.7%) had more than one autistic sibling tends to support our previous findings that there may be a genetically determined subtype of autism (28–31).

We hope that the results of our study will provide a definitive bench mark for planning services and setting public health and research priorities throughout the world.

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Identification of Borderline Personality Disorder With the NIMH Diagnostic Interview Schedule

Marvin S. Swartz, M.D., Dan G. Blazer, M.D., Ph.D., Linda K. George, Ph.D.,
Idee Winfield, Ph.D., James Zakris, M.D., and Ellen Dye, Ph.D.

No lay-administered interviews are currently available to identify persons with borderline personality disorder. The authors studied 79 subjects with the NIMH Diagnostic Interview Schedule (DIS), a lay-administered interview, and the Diagnostic Interview for Borderline Patients (DIB) and used the results to construct a DIS-based diagnostic index to identify borderline personality disorder. Using the clinician-administered DIB as the diagnostic standard, the authors found that the DIS borderline index had a sensitivity of 85.7%, a specificity of 86.2%, and a kappa of 0.67. The DIS borderline index is a promising extension of the DIS that will facilitate studies of borderline personality disorder in clinical and community settings.

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Borderline personality disorder is a clinically recognized and relatively well-defined personality disorder characterized by potentially self-damaging impulsivity and unpredictable behavior, unstable and intense interpersonal relationships, inappropriate intense anger or lack of control of anger, identity disturbance, affective instability, intolerance of being alone, physically self-damaging acts, and chronic feelings of emptiness. Gunderson and Kolb (1) identified the discriminating features of borderline personality disorder by clinical consensus regarding prototypical borderline patients. Subsequently, they developed the Diagnostic Interview for Borderline Patients (DIB) (2, 3), a semi-structured clinician-administered interview. Gunderson's diagnostic scheme for borderline patients was modified in *DSM-III* to exclude the criteria of brief

psychotic phenomena, depersonalization, and derealization (4-6). Although the DIB and *DSM-III* categorizations of borderline personality disorder are somewhat discordant, the DIB remains an excellent standard for structured assessment of the diagnosis in clinical research settings (7-11).

Previous studies (6, 7, 9) reported substantial agreement on the diagnosis of borderline personality disorder between interviews by clinicians who apply *DSM-III* criteria and diagnoses based on the DIB (mean kappa, approximately 0.70). Sensitivities and specificities for the DIB, determined on the basis of the clinical *DSM-III* borderline personality disorder diagnosis as the true arbiter of the diagnosis, yield sensitivities of 70%-90% and specificities of 60% to more than 90% (6, 7, 9, 10); however, agreement between the DIB and *DSM-III*-guided clinical assessment is a better measure of the diagnostic utility of the DIB. *DSM-III* criteria, as applied by trained clinicians, cannot be considered a better standard for the diagnosis than the DIB because there are no data indicating superiority of one to the other. Both the DIB and the *DSM-III* criteria capture the core features of a group of patients clinically identified as borderline by clinicians (6, 7).

During the past decade, a number of general diagnostic interviews have been developed, including the Present State Examination (12), the Schedule for Affective Disorders and Schizophrenia (SADS) (13), the Structured Clinical Interview for *DSM-III* (14), and the NIMH Diagnostic Interview Schedule (DIS) (15), a highly structured lay-administered interview used in the NIMH-sponsored Epidemiologic Catchment Area Program (16).

The development of the DIS has made community studies of certain axis I *DSM-III* disorders as well as antisocial personality disorder possible. Although symptoms on the DIS may be analyzed by preexisting DIS/*DSM-III* diagnostic algorithms, symptoms may also be analyzed independently to identify other potential symptom profiles. Given the widespread clinical and epidemiologic use of the DIS, we examined whether a symptom profile on the DIS could be used to identify borderline patients. Specifically, if the DIB were used as the arbiter of the borderline diagnosis, could a symptom profile on the DIS identify a comparable group of subjects? Loranger et al. (11) found that the

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SADS, a clinician-administered interview, elicits responses used by the DIB scoring algorithm to assess borderline personality disorder. Thus, a slight extension of the SADS, intended to probe for areas relevant to social adaptation, can enable the SADS to be used to identify borderline patients. Similar logic may extend to the DIS.

The DIS, a lay-administered interview designed for use in epidemiologic studies, generates computer-based diagnoses of selected *DSM-III* disorders (15). The DIS takes 2 hours or more to administer and is designed to elicit the elements of a diagnosis, including the presence or absence of symptoms, their severity, frequency, and distribution over time, and whether or not they can be explained by a physical illness, drug or alcohol abuse, or other psychiatric diagnoses. Both current and lifetime diagnoses can be generated. For the present study, the DIS was abbreviated to elicit current diagnoses (including generalized anxiety disorder); however, certain lifetime diagnoses (e.g., schizophrenia) were also elicited. In contrast to the DIS, the DIB is a clinician-administered instrument that diagnoses borderline personality disorder by the Gunderson criteria (3); it can be administered reliably by nonprofessionals (17) but generally has been administered by experienced clinicians. The interview takes approximately 1 hour and directs the interviewer to probe 123 items intended to allow the interviewer to assess 29 summary statements that sample behavior, affects, and cognitions thought to exemplify the diagnosis. A careful comparison of the DIS and the DIB demonstrates considerable overlap in eliciting symptoms relevant to the diagnosis of borderline personality disorder.

With the exception of antisocial personality disorder, the DIS is not intended to assess personality disorders. Hence, no lay-administered method of diagnosing borderline personality disorder is available. All borderline diagnostic instruments are designed for use by trained clinicians, and their cost is prohibitive in community studies. Development of a borderline diagnostic algorithm for the lay-administered, computer-scored, and widely used DIS would make community studies of borderline personality disorder feasible and permit use of the DIS for diagnosis in clinical settings.

The present study was designed to determine whether the lay-administered DIS could identify borderline patients according to the criteria of Gunderson as operationalized in the clinician-administered DIB (3). Furthermore, using the DIB as the diagnostic standard, we sought to construct a diagnostic algorithm for the DIS that would yield acceptable measures of diagnostic concordance, sensitivity, and specificity for the diagnosis of borderline personality disorder.

METHOD

To develop a DIS-based borderline personality disorder algorithm (DIS borderline index), we recruited

TABLE 1. Demographic Characteristics of 60 Nonpsychotic Psychiatric Patients and 19 Normal Subjects

Characteristic ^a	N	%
Sex		
Male	23	29.1
Female	56	70.9
Race		
White	71	89.9
Black	8	10.1
Marital status		
Never married	28	35.4
Married	36	45.6
Separated or divorced	15	19.0
Residence		
Urban	69	87.3
Rural	10	12.7
Vocational status		
Homemaker	6	7.6
Student	12	15.1
Employed	50	63.3
Retired or disabled	10	12.7
Unemployed	1	1.3

^aSubjects were 18–55 years old.

79 patients from the Duke University Medical Center. The sample, drawn to include a spectrum of psychopathology, included 32 acute psychiatric inpatients, 28 psychiatric outpatients, and 19 normal subjects. The 32 inpatients were selected from all consecutive admissions of 18- to 55-year-old nonpsychotic patients to the acute psychiatric service (a 20-bed unit with an average length of stay of 27 days per patient). When patients were unavailable for interview on this service, consecutive admissions were recruited from an alternate inpatient service. Patients were referred to the study by the head nurse of the acute psychiatric service who was blind to the study design and reported to study personnel that a nonpsychotic, potentially cooperative, 18- to 55-year-old was available for study. The 28 outpatients were recruited in a similar manner from the psychiatry outpatient clinics (general evaluation and treatment clinics). Finally, 19 normal subjects were recruited from the Duke Center for the Study of Aging, which maintains a pool of available adult subjects of all ages for studies in the center. Normal subjects were randomly selected from this subject pool to obtain subjects between the ages of 18 to 55 years; however, younger subjects (aged 18–25) were not readily available from this subject pool and were recruited through general advertisements at Duke University. Noninpatient subjects were approached by one of the study personnel (E.D.) for participation in the study and briefly screened to exclude psychosis. Consent was obtained from the subjects, and the interviews were administered in an identical manner for inpatients and outpatients. The mean \pm SD age of the 79 subjects was 31.4 ± 8.2 years. The demographic characteristics of the sample are presented in table 1.

Each patient was interviewed with the DIB and the DIS in a random sequence. The DIB was individually administered by two members of the research team

TABLE 2. DIS/DSM-III Diagnoses for 60 Psychiatric Patients and 19 Normal Subjects

Diagnosis	Past Year		Current	
	N	%	N	%
Major depression	41	51.9	35	44.3
Generalized anxiety disorder	36	45.6	24	30.4
Panic disorder	25	31.6	22	27.8
Dysthymic disorder	23	29.1	20	25.3
Drug abuse/dependence	6	7.6	6	7.6
Alcohol abuse/dependence	5	6.3	5	6.3
Mania	2	2.5	2	2.5
Obsessive-compulsive disorder	1	1.3	1	1.3
Schizophrenia	0	0.0	0	0.0
Somatization disorder	0	0.0	0	0.0
Antisocial personality disorder	0	0.0	0	0.0
Agoraphobia	0	0.0	0	0.0
Anorexia nervosa	0	0.0	0	0.0

(M.S.S. and J.Z.), who achieved satisfactory interrater reliability ($\kappa=0.79$); one of the interviewers (M.S.S.) was trained by Gunderson ($\kappa=0.81$). The DIS was administered by an interviewer (E.D.) trained by experienced interviewers from the Duke site of the Epidemiologic Catchment Area Program. The study personnel were blind to the diagnostic status of the patients and the results of other interviews.

The DIB was scored according to the scoring algorithm designed by Gunderson (3). By this scoring algorithm, a patient can achieve a score between 0 and 10. Most studies have adopted a criterion score of 7 or more to provide an optimal balance of sensitivity and specificity in differentiating patients with borderline personality disorder from those without borderline personality disorder. The DIS is structured for both questions and probes and is precoded so that responses are data-entered directly after editing; however, because the DIS was modified for the present study to elicit current diagnoses, the hand-scoring manual for the DIS was employed.

RESULTS

Many of the 60 psychiatric patients had multiple DIS/DSM-III diagnoses particularly because hierarchical exclusion criteria were not used. Their most common current diagnoses were major depression (44.3%), generalized anxiety disorder (30.4%), panic disorder (27.8%), and dysthymic disorder (25.3%) (table 2). Schizophrenia was underrepresented, in part because active psychosis was an exclusion criterion. Other diagnoses were underrepresented probably because they are treated in other inpatient and outpatient settings and are generally less common. None of the 19 normal subjects met DIS/DSM-III criteria for a diagnosis.

Twenty-one patients scored 7 or higher on the DIB and were diagnosed as having borderline personality disorder. Of the 32 inpatients, 17 had borderline personality disorder, as did four of the 28 outpatients.

Although the proportion of borderline diagnoses among the inpatients may seem high, it may not be unusual among nonpsychotic patients on an adult acute ward. The demographic characteristics of borderline and nonborderline patients were similar and did not differ appreciably with regard to sex, age, marital status, type of residence, or employment status. Differences were evident with regard to comorbidity. In the past year, the borderline patients were significantly more likely than the nonborderline patients to be diagnosed with major depression (80.9% and 11.4%, respectively; $\chi^2=9.67$, $df=1$, $p<0.005$), generalized anxiety disorder (85.7% and 31.0%; $\chi^2=18.58$, $df=1$, $p<0.001$), panic disorder (61.7% and 20.7%; $\chi^2=12.11$, $df=1$, $p<0.001$), dysthymia (52.4% and 20.7%; $\chi^2=7.50$, $df=1$, $p<0.01$), drug abuse/dependence (19.0% and 3.5%; $\chi^2=5.39$, $df=1$, $p<0.05$), and alcohol abuse/dependence (23.8% and 0.0%; $\chi^2=14.74$, $df=1$, $p<0.001$). Thus, the borderline patients were more impaired and hence diagnosed as having multiple disorders.

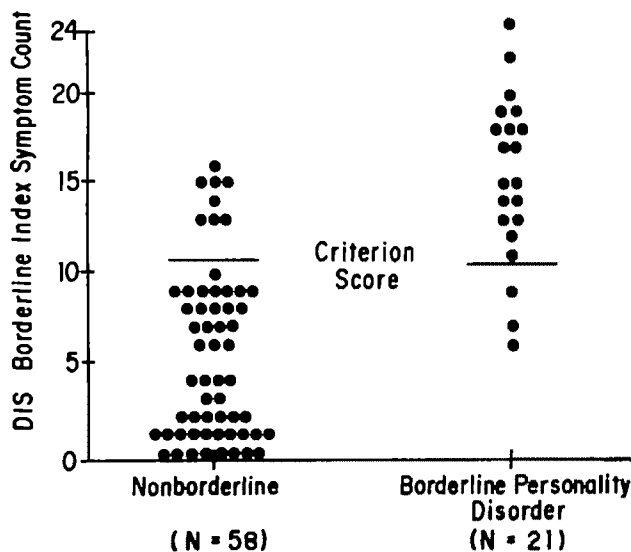
DEVELOPMENT OF DIS BORDERLINE INDEX

The DIS borderline index was constructed in two stages. Initially, DIS symptoms were paired with DIB items to construct a set of DIS symptoms with the greatest face validity for the DIB borderline diagnosis. Gunderson (personal communication, 1986) concurred that the DIS symptom list elicits most symptoms examined in the DIB. Chi-square analyses were used to test the association of DIS symptoms with the DIB borderline diagnosis. A subset of 24 DIS symptoms highly associated with borderline personality disorder was selected to construct the DIS borderline index. The index was designed to optimize the statistical association of the DIS symptoms with the diagnosis while maintaining the face validity from the preliminary index. Some symptoms were deleted because of potential redundancy that might lend excessive weight to certain types of symptoms. For example, although most depressive symptoms were associated with the borderline diagnosis, a subset was retained to optimally weight depressive symptoms. Table 3 lists the current DIS symptom (in the past year) for the 24-symptom DIS borderline index and its association with the borderline diagnosis. The list includes symptoms of anxiety, depression, suicidality, irritability, impulsivity, interpersonal difficulties, and brief psychotic phenomena. All items but one ("hitting partner in fight"), retained because of its ability to probe for stormy intimate relationships, were strongly associated with the borderline diagnosis.

As illustrated in figure 1, most of the nonborderline subjects had fewer than 10 DIS borderline index symptoms, whereas the borderline patients generally reported more than 10 symptoms. A criterion score of 11 or more symptoms yielded optimal discrimination between borderline and nonborderline patients. The cri-

TABLE 3. DIS Borderline Index Symptoms Among 60 Psychiatric Patients and 19 Normal Subjects With or Without DIB-Diagnosed Borderline Personality Disorder

DIS Symptom Within Past Year ^a	Borderline Group (N=21)		Nonborderline Group (N=58)		Association With Borderline Diagnosis	
	N	%	N	%	χ^2 (df=1)	p
Anxiety attacks	16	76.2	17	29.3	13.93	0.0002
Anxiety for 1 month or more	19	90.4	22	37.9	17.05	0.0001
Tenseness or jumpiness	17	80.9	16	27.5	13.92	0.0002
Irritability or edginess	19	90.4	21	36.2	17.10	0.0001
Three or more depressive symptoms ^b	21	100.0	34	58.6	12.48	0.0004
Sleeping too much	15	71.4	14	24.1	14.43	0.0001
Worthlessness	17	80.9	22	37.9	11.42	0.0007
Thoughts of death	17	80.9	21	36.2	12.36	0.0004
Wanting to die	15	71.4	14	24.1	14.84	0.0001
Thoughts of suicide	18	85.7	24	41.4	12.17	0.0005
Suicide attempt	11	52.4	50	8.6	18.28	0.0001
Hopelessness	18	85.7	22	39.7	13.10	0.0003
Spending sprees	5	23.8	10	1.7	10.71	0.001
Increased libido	9	42.9	50	8.6	12.39	0.0004
Distractibility	16	76.2	13	22.4	21.15	0.0002
Hitting partner in a fight	11	52.4	21	36.2	4.67	0.20
Lying a lot as an adult	12	57.1	50	8.6	21.49	0.0001
Using weapon in a fight	4	19.0	1	1.7	7.80	0.005
Fear of being alone	12	57.1	11	19.0	10.89	0.001
Amnesic periods	7	33.3	2	3.5	13.64	0.0002
Unusual spells	8	38.1	3	5.2	13.94	0.0002
Giving up work due to somatic symptoms	11	57.1	10	17.2	12.22	0.005
Feelings of being followed (transient)	8	38.1	5	8.6	9.74	0.008
Hearing things (transient)	6	28.6	3	3.5	10.69	0.001

^aComplete queries for DIS symptoms are available from the authors.^bSummary variable of three or more depressive symptoms.**FIGURE 1. Distribution of DIS Borderline Index Symptoms Among 60 Psychiatric Patients and 19 Normal Subjects With or Without DIB-Diagnosed Borderline Personality Disorder**

terion score of 11 of 24 DIS items correctly identified 18 of the 21 DIB borderline patients and 50 of the 58 nonborderline patients, yielding a sensitivity of 85.7%, a specificity of 86.2%, a positive predictive power of 69.2% (18 of 26), a negative predictive power of 94.3% (50 of 53), an overall diagnostic power of 86.1% (68 of 79), and a kappa of 0.67. Thus, in a sample with a rel-

atively high prevalence of DIB borderline patients (21 of 79 or 26.6%) and fair diagnostic complexity, the DIS borderline index performed well.

DISCUSSION

We designed this study to determine whether the lay-administered DIS could be used to diagnose borderline personality disorder. We began with the assumption that a latent syndrome (or syndromes) resembling borderline personality disorder is embedded in the symptom information elicited for specific DIS diagnoses. In a previous study (18), we examined the latent structure (or underlying relationships) of antisocial and related symptoms in a community sample from the Duke Epidemiologic Catchment Area Program and found two symptom profiles that resembled borderline spectrum disorders. Using a "fuzzy" set clustering technique, which creates nonmutually exclusive symptom clusters, we found a female-associated symptom profile characterized by marital instability, other domestic problems, and occupational difficulties and a male-associated symptom profile characterized by antisocial behavior, multiple affective symptoms, drug abuse, and marital instability and resembling a mixed personality disorder with antisocial and borderline features. Thus, we hypothesized that a symptom profile resembling borderline personality disorder could be identified with the DIS.

In the present clinical study, direct comparison of

DIS symptom profiles and the DIB borderline diagnosis illustrated that a DIS borderline diagnosis can be identified. Using a criterion score of 11 of 24 items allows diagnostic precision comparable and in many cases better than other DIS/*DSM-III* diagnoses (15). The performance of the DIS borderline index should be interpreted with caution. Because the index was extracted from the body of the DIS, it has not been tested as a separate instrument and is not intended for such use. For example, one item in the index (three or more depressive symptoms) is a summary variable that requires administration of the entire DIS section on depression.

The index must be considered preliminary until it has been tested in another patient sample. The present sample was drawn to minimize sampling bias but did not include a full range of psychopathology. Specifically, individuals with substance abuse, eating disorders, and antisocial personality disorders were underrepresented in this sample, and the ability of the index to discriminate, for example, nonborderline from borderline substance abusers is untested. Similarly, the addition of patients with antisocial personality would help to test the discriminant validity of the index. Another sample of subjects, perhaps from a different setting, would help to refine the index.

The index employs symptom queries for psychopathologic states in an effort to identify a trait disorder, an approach that risks mistaking state (e.g., depression) for trait (e.g., borderline personality disorder). Furthermore, the trait items included come from the section on antisocial behavior and risk inappropriate inclusion of antisocial individuals. Also, the index examines few items that indicate interpersonal difficulties, which are important features of the disorder.

Some clinicians would eschew the use of lay interviewers to diagnose borderline personality disorder. Historically, the borderline construct has relied heavily on clinical inference to detect core features such as identity diffusion, use of primitive defenses, and intrapsychic splitting. However, an examination of more structured interviews, such as the DIB, reveals that much of the inference in the diagnosis has been reduced and most symptomatic evidence of the diagnosis is readily observable. For example, although the DIB examines interpersonal manipulateness, the DIS probe examining deceitfulness as an adult (have you found you have lied a lot as an adult?) serves as a good proxy for manipulateness. The present DIS borderline index designed for use by lay interviewers may well miss less florid manifestations of borderline personality disorder, but in less severe cases, clinicians would also be less reliable. Similarly, although the DIS borderline index may fail to diagnose mild forms of the disorder, many such individuals would not meet DIB or *DSM-III* criteria for the disorder.

In the present clinical study, the DIS borderline index performed well, yielding high sensitivity, specificity, and good agreement with the clinical borderline diagnosis. Further studies are required to demonstrate

its reliability in community samples. We expect the index to perform somewhat differently in community studies where fewer subjects will have psychiatric disorders and those afflicted would be less severely ill; in such a setting, we expect the sensitivity of the DIS borderline index to be somewhat lower but the specificity to be considerably higher when challenged by less complicated cases.

The addition of the DIS borderline diagnosis will allow reexamination of heterogeneous axis I disorders to determine whether demographics, risk factors, and other correlates of major depression and other axis I disorders differ according to their association with or independence from personality disorders. Testing the reliability of the DIS borderline index in clinical and community samples with the aim of incorporating it as a diagnostic algorithm of the DIS will help to achieve an important goal: expanding the use of the DIS to permit a fuller examination of the interaction of axis I and axis II *DSM-III* disorders, previously limited on axis II to antisocial personality disorder.

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Premorbid Sociosexual Functioning and Long-Term Outcome in Schizophrenia

Richard S.E. Keefe, M.A., Richard C. Mohs, Ph.D.,
Miklos F. Losonczy, M.D., Ph.D., Michael Davidson, M.D.,
Jeremy M. Silverman, Ph.D., Thomas B. Horvath, M.D., and Kenneth L. Davis, M.D.

Chronic schizophrenic patients with the most severe social deterioration have been shown to differ from other chronic schizophrenic patients with respect to measures of left-to-right ventricular asymmetry, negative symptoms, and response to haloperidol treatment. In the current study, the authors investigated the social antecedents of these characteristics of very poor outcome schizophrenia in 69 chronic schizophrenic patients. Poor premorbid sociosexual functioning was associated with more severe left-to-right ventricular asymmetry, greater severity of negative symptoms, fewer positive symptoms, and worse current social functioning. These data suggest that factors associated with severe social deterioration in the end stage of schizophrenia are also associated with premorbid sociosexual impairment.

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Impaired social adjustment in individuals with schizophrenia has been demonstrated repeatedly. Schizophrenic patients have shown more social impairment after the onset of their disorder than individuals with other psychiatric disorders and than normal control subjects (1-5), and the level of their premorbid social adjustment has also been shown to be significantly lower than that of either of these groups (6-9). These results are consistent with the notion that poor premorbid social functioning in schizophrenic patients is an early manifestation of schizophrenia or that it is a vulnerability factor of the disorder (10, 11).

Schizophrenic patients who demonstrate social difficulties before their first psychotic episode have been shown to differ from other schizophrenic patients on several measures. These patients demonstrated a more

chronic course (12, 13), poorer response to neuroleptic treatment (14), poorer social outcome (15, 16), more severe CT scan abnormalities (17), a higher prevalence of tardive dyskinesia (18), higher accumulations of CSF homovanillic acid (19), and more neurological soft signs (20). However, the relationship between poor premorbid functioning and these characteristics has not been supported by all studies (21).

Schizophrenic patients with the worst social outcome, who had been fully dependent on others for their survival, were shown by previous studies from our center to differ from other schizophrenic patients with respect to several important antecedent, concurrent, and prospective measures (22, 23). These patients had more ventricular abnormalities and more severe negative symptoms and did not respond to haloperidol treatment, and their first-degree relatives had a greater morbid risk for schizophrenia spectrum disorders. The direction of causality involved in these relationships remains uncertain. Ideally, longitudinal studies designed to assess these variables throughout the life span of a schizophrenic patient could determine the direction of causality between severe social deterioration in the end stage of schizophrenia and the results of concurrent and prospective measures, such as ventricular abnormalities, negative symptoms, and failure to respond to neuroleptic treatment. However, in the absence of such studies, assessment of premorbid social impairment in a group of schizophrenic patients, including those with the most severe current social deterioration, could help promote an understanding of the relationship between concurrent characteristics of very poor outcome schizophrenia and social behavior before the devastating effects of frank psychosis and its treatment have emerged. Toward this end, we investigated the hypothesis that the results of concurrent and prospective measures demonstrated to be characteristic of schizophrenic patients with the poorest social outcome would be associated with poor premorbid sociosexual functioning. Our specific expectations were that patients with worse premorbid sociosexual functioning would demonstrate worse current social functioning, more severe negative symptoms, more ventricular abnormalities, and less of a response

Received Dec. 14, 1987; revision received Aug. 9, 1988; accepted Aug. 18, 1988. From the Psychiatry Service, VA Medical Center, and the Department of Psychiatry, The Mount Sinai School of Medicine, New York, N.Y. Address reprint requests to Mr. Keefe, Psychiatry Service (116A), VA Medical Center, 130 West Kingsbridge Rd., Bronx, NY 10468.

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to haloperidol treatment than other schizophrenic patients.

METHOD

We studied 69 chronic schizophrenic men ranging in age from 22–65 years ($\text{mean} \pm \text{SD} = 37.6 \pm 11.4$ years) who were admitted to the Schizophrenia Biological Research Center of the Bronx Veterans Administration Medical Center or the Mount Sinai School of Medicine. All patients were judged by an attending physician to require hospitalization. Patients with chronic medical illness or substance abuse were excluded from the study, although 33% of the patients studied had met Research Diagnostic Criteria (RDC) (24) for alcoholism or drug use disorder in the past. Informed consent was obtained from the patient or from a first-degree relative if an otherwise assenting patient was unable to give true informed consent. The diagnosis of schizophrenia was based on the consensus of two raters using the structured interview of the Schedule for Affective Disorders and Schizophrenia (SADS) (25). All patients met criteria for definite schizophrenia or schizoaffective disorder, mainly schizophrenic, according to RDC or definite schizophrenia according to the Feighner diagnostic system (26). Kappa coefficient correlations between the two raters were 0.91 for the RDC and 0.90 for the Feighner diagnoses.

Premorbid Asociosexual Functioning

Premorbid social and sexual dysfunction was assessed in all patients with the Premorbid Asocial Adjustment Scale (13), which consists of seven items, each scored from 1 to 7. A set of scoring guidelines is included with each item of the scale. The premorbid asociosexual functioning item, referred to as "sociosexual adjustment" on the scale, is rated for the period of time when the patient was 16–20 years old. For each patient, ratings of premorbid asocial adjustment were obtained by two independent raters from at least two informants who had observed the patient frequently during the premorbid period. The reliability of each informant was rated on a scale of 1 (very good) to 5 (very poor); reliability ratings of 1–3 were considered adequate. In a previous report on a subgroup ($N=45$) of this cohort (27), interrater reliability was found to be high for all items of the Premorbid Asocial Adjustment Scale, but agreement between informants was found to be adequate only for the premorbid asociosexual functioning item ($\text{ICC}=0.82$, $\text{df}=1, 43$, $p<0.01$). All other items on this scale did not demonstrate significant interinformant reliability. Because these data indicate that only the item on sociosexual adjustment is a reliable indicator of premorbid adjustment and because of reports from other investigations that prediction from premorbid data is more successful with individual characteristics than with a comprehen-

TABLE 1. Premorbid Asociosexual Functioning of 69 Chronic Schizophrenic Men^a

Sociosexual Adjustment ^b Score	Description	N
1	Healthy interest in girls, steady close relationships with sexual intercourse or sexual play, went out with girls regularly, steady close relationships with little or no sexual play	16
2	Went out with girls regularly, steady casual relationships with or without sexual play or intercourse	12
3	Went out with girls regularly, passing casual relationships with or without sexual play or intercourse	10
4	Casual occasional contact with girls with or without sexual intercourse or sexual play	16
5	Interested in girls, but never went out on dates	11
6	No sexual interests in either sex	4

^aData obtained by two independent raters from at least two informants who had observed the patient frequently during the premorbid period (i.e., when the patient was 16–20 years old).

^bThe only one of seven items on the Premorbid Asocial Adjustment Scale (13) for which agreement between informants had been found to be adequate (27).

sive prognostic scale (16, 28), data analysis included only the premorbid asociosexual functioning item.

Score definition for premorbid asociosexual functioning and distribution among our 69 patients are presented in table 1. The original scale included an additional rating of "homosexual involvement only," which was given a score of 6; "no sexual interests in either sex" was scored as a 7. Because the "homosexual involvement only" rating was viewed as a disruption of the quantitative nature of this measure, it was excluded from the measure, and "no sexual interests" was scored as a 6. The result of this transformation of the data was an ordinal scale on which increasing scores were associated with less sociosexual involvement. The one patient who was rated as having "homosexual involvement only" on the scale was excluded from the study. The distribution of the scores among our patients was moderately positively skewed (table 1); the $\text{mean} \pm \text{SD}$ score for the item was 2.99 ± 1.58 .

Clinical Description

Data regarding several clinical variables were obtained by two independent raters. Current social and occupational functioning and severity of symptoms were assessed with the Levels of Functioning Scale (28) ($\text{ICC}=0.91$, $\text{df}=1, 67$, $p<0.001$) by summing items rating the number and quality of social contacts, duration of nonhospitalization during the past year, work history in the past year, overall symptom severity in the past month, and overall "quality of life." Positive symptom severity scores (29) ($\text{ICC}=0.82$, $\text{df}=1, 67$, $p<0.001$), which estimate scores obtained from

the Scale for the Assessment of Positive Symptoms (30), were determined by summing SADS items rating severity of hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Number of positive symptoms was determined by summing the number of RDC schizophrenic symptoms (the "A" criteria) manifested ($ICC=0.79$, $df=1$, 67 , $p<0.001$). Negative symptoms were assessed in 36 patients by determining total scores (excluding global and subjective rating scores) on the Scale for the Assessment of Negative Symptoms (31) ($ICC=0.82$, $df=1$, 34 , $p<0.001$). Negative symptom severity scores (29) ($ICC=0.82$, $df=1$, 67 , $p<0.001$) were assessed for the entire cohort by using the items from the SADS, Levels of Functioning Scale, and the Thought, Language, and Communication Scale (32) that corresponded to 16 of the 30 items on the negative symptoms scale. Negative symptom severity scores and negative symptom scale total scores were found to be highly correlated ($r=0.73$, $df=34$, $p<0.001$) in patients for whom both scores were available. Overall severity of psychopathology was assessed by Clinical Global Impression (CGI) scores ($ICC=0.75$, $df=1$, 67 , $p<0.001$). Data on age at onset, number of psychiatric hospitalizations, total time in psychiatric hospitals, number of years ill, and educational level were available for all patients. Consensus scores and diagnoses were determined by the two independent raters and an independent diagnostic "expert," who resolved any disagreements.

Cerebral Ventricle Measures

Ventricle-brain ratio (VBR) and ventricular asymmetry were determined from CT scans on a high-resolution Technicon 2020 scanner of 43 of our 69 patients. Since these ventricular measures are considered to be unrelated to whether the patient is in an exacerbated or stable state, 10 additional schizophrenic patients who did not require hospitalization and were considered to be in a state of remission relative to their periods of acute exacerbation were included in this part of the study. Therefore, ventricular measures were obtained on a total of 53 schizophrenic patients. Premorbid asocial functioning scores did not differ significantly between these 53 patients and those patients for whom ventricular measures were not available (3.40 and 2.74, respectively; $t=1.67$, $df=67$, $p=0.10$).

The method used for determining VBR has been described in detail elsewhere (22). To calculate ventricular asymmetry, the left VBR was divided by the right VBR, resulting in a left-to-right lateral ventricular ratio determined by two separate raters. The mean of this ratio determined by both raters was used in subsequent calculations.

Haloperidol Treatment Response

Thirty-eight patients underwent a standardized dose schedule of haloperidol to determine degree of treatment response. All patients received 10 mg b.i.d. of

haloperidol for 28 days. If patients were not responsive, haloperidol dose was increased to 15 mg b.i.d. until day 36, at which time it was increased to 20 mg b.i.d. until day 43. Brief Psychiatric Rating Scale (BPRS) (33) scores were obtained weekly by two independent raters. A baseline BPRS score was determined by calculating the mean of four scores acquired over a 2-week drug-free period before haloperidol administration. The degree of treatment response was determined by the decrease in BPRS score from baseline to the last day of the study. The interrater reliability of BPRS change was high ($ICC=0.94$, $df=1$, 36 , $p<0.001$).

RESULTS

Higher premorbid asociosexual functioning scores, suggesting lower levels of social and sexual activity before the onset of schizophrenia, were found to correlate significantly with lower levels of current social and occupational functioning and severity of symptoms as determined by the Levels of Functioning Scale total scores ($r=-0.26$, $df=67$, $p<0.03$), current number of social contacts ($r=-0.51$, $df=67$, $p<0.001$), and quality of social contacts ($r=-0.34$, $df=67$, $p<0.005$). Higher premorbid asociosexual functioning scores also correlated significantly with greater overall severity of psychopathology as assessed by the CGI ($r=0.25$, $df=67$, $p<0.05$), a greater severity of negative symptoms as assessed by negative symptom severity scores ($r=0.32$, $df=67$, $p<0.01$), and fewer positive symptoms as determined by the number of RDC schizophrenia symptoms manifested ($r=-0.29$, $df=67$, $p<0.03$). The correlation between premorbid asociosexual functioning scores and severity of negative symptoms as determined by the Scale for the Assessment of Negative Symptoms total scores was not significant ($r=0.25$, $df=34$, $p<0.15$); however, scores were available for only 36 of the patients in this study, which resulted in a considerable loss of statistical power for this analysis. There was no significant correlation between premorbid asociosexual functioning scores and severity of positive symptoms as determined by scores estimating the Scale for the Assessment of Positive Symptoms from SADS items. Premorbid asociosexual functioning scores were not significantly correlated with age, age at onset, number of psychiatric hospitalizations, total time in psychiatric hospitals, number of years ill, or educational level.

Premorbid asociosexual functioning scores correlated significantly with the degree of left-to-right lateral ventricular asymmetry, which was calculated by dividing the left VBR by the right VBR ($r=0.28$, $df=51$, $p<0.05$). Thus, greater premorbid sociosexual impairment was associated with greater left-to-right ventricular asymmetry. VBR was not significantly correlated with premorbid asociosexual functioning scores. Symptom improvement during haloperidol treatment, measured in 38 patients by the decrease in total BPRS

score from baseline to the last day of the study, covaried for baseline BPRS score, was not significantly related to premorbid asociosexual functioning scores (partial $r = -0.20$, $df = 35$, $p = 0.12$). The patients with past RDC diagnoses of alcoholism or drug use disorder were not significantly different from the other schizophrenic patients on any of the measures investigated. In addition, removing these patients from our sample did not substantially alter the magnitude of the correlations reported.

DISCUSSION

In our group of chronic schizophrenic men, poor premorbid sociosexual functioning was associated with greater current severity of negative symptoms, fewer positive symptoms, greater overall severity of psychopathology, worse current social and occupational functioning, and left-to-right lateral ventricular asymmetry but not significantly associated with symptom improvement during haloperidol treatment. These data support the hypothesis that the results of many of the concurrent measures previously demonstrated to be characteristic of schizophrenic patients with the poorest social outcome (22, 23) are associated with poor premorbid sociosexual functioning.

The correlation of current negative symptoms, social impairment, and overall level of current psychopathology with poor premorbid sociosexual adjustment is consistent with the notion that schizophrenic patients with the worst social outcome differ from other schizophrenic patients not as a result of social deterioration after the onset of their psychosis but because of dispositional factors. The etiologic relationship of prepsychotic sociosexual functioning and schizophrenic outcome is difficult to specify because asociality before the onset of schizophrenia is often indistinguishable from early onset of illness manifested as social impairment during the prodromal period. Poor sociosexual adjustment during adolescence in schizophrenic patients can be distinguished from manifestations of the illness only if diagnostic criteria are used that require psychotic symptoms. Kraepelin's description of the course of dementia praecox (34) focused on the notion that the core features of the illness are the enduring negative symptoms or deficit traits that often precede psychosis for years; these symptoms have also been considered by others to be those most characteristic of schizophrenia (35). Early sociosexual impairment of some schizophrenic patients could be either part of their premorbid personalities or a vulnerability factor to the disorder, but at least a few patients may have had sociosexual difficulties during the prepsychotic period as a result of an early onset of schizophrenia. In the latter instance, the relationship between early sociosexual and current social impairment is more of a reflection of the stability of poor social functioning throughout the course of the schizophrenic illness than it is an indication of a predictor of current functioning

based on the assessment of an unaffected premorbid personality. This interpretation of the data suggests that patients who demonstrate an earlier onset of such negative symptoms as sociosexual withdrawal are more likely to demonstrate severe social withdrawal in the later stages of their illness. Hence, regardless of whether sociosexual impairment before the onset of psychosis is viewed as part of a schizophrenic individual's predisposition to the illness or as an early expression of the disorder, the data we present are consistent with the notion that severe social deterioration in the end stage of schizophrenia is a result of predisposing factors.

The correlation of premorbid asociosexual functioning with greater overall level of psychopathology is consistent with previous reports that premorbid asociality predicts a poor prognosis (12, 13). This finding should not, however, be interpreted to indicate that patients with poor premorbid social histories demonstrate greater psychopathology in all areas. In fact, such patients manifested fewer positive symptoms than patients with better premorbid histories. A possible explanation for this finding is that the presence of negative symptoms, especially social withdrawal and deterioration, is viewed as particularly important in the formation of a global clinical impression.

A relationship between poor premorbid social functioning and large VBR has been previously reported by several investigators (17, 36, 37) but not found by others (38–40). This relationship suggests a possible structural defect in patients with poor premorbid histories. Our finding in this study that poor premorbid sociosexual history was associated with asymmetrical cerebral ventricles is consistent with 1) previous reports of an association between the absence of normal left occipital asymmetry and greater psychopathology in schizophrenic patients (41), 2) reports of schizophrenic patients with increased incidences of reversal of normal anatomical asymmetries (42, 43), anterior left hemisphere atrophy (44), and diminished left caudate function on metabolic positron emission tomography (45), and 3) postmortem findings of decreased cortical width in the left parahippocampal gyrus (46). Hence, the purported left-sided brain abnormality in schizophrenia may be more common in patients with poor premorbid sociosexual histories. In the absence of replication by other investigators, this relationship should be viewed cautiously, particularly since some degree of ventricular asymmetry has been reported in a group of healthy, normal subjects (47).

This study has some limitations due to sample size, the population studied, and the procedures required for obtaining historical information. The low correlation between premorbid sociosexual impairment and treatment response could be attributed in part to the overall poor response to treatment in this group of chronic Veterans Administration patients with schizophrenia. Also, since only 38 patients entered into this part of the study, adequate statistical power may not have been available to detect the relationship between

premorbid social factors and later treatment response demonstrated by other investigators (14). Schizophrenic patients with a very early age at onset were presumably excluded from the study by Armed Forces screening procedures. Thus, the patient sample in this study was limited to patients with a later onset of psychosis whose illness followed a chronic course; including a broader range of patients may have increased the number of relationships that we found. Hence, even among patients healthy enough to pass Armed Forces screening tests, premorbid sociosexual impairment was associated with later characteristics of very poor outcome schizophrenia.

In a previous report on a subgroup of the cohort investigated in this study (27), six of the seven items of the Premorbid Asocial Adjustment Scale demonstrated inadequate agreement among informants. The only item that demonstrated both adequate interinformant agreement and interrater reliability was the assessment of premorbid sociosexual functioning. Thus, in this study, only this item was used. Although the reliability of this item has been established, the use of only one item to measure a construct limits the depth and accuracy of this measure, and the findings of this study are qualified by this limitation. However, the superior predictive value of individual characteristics over comprehensive prognostic scales has been found by other investigators (16, 28). The need for further investigation of the relationship between premorbid social factors and later characteristics of schizophrenia using a more extensive, yet reliable, independent measure is clear.

In summary, these data are consistent with the notion that the concurrent characteristics of very poor outcome schizophrenic patients are not solely a result of the chronicity of these patients but, rather, are associated with antecedent factors. Thus, poor premorbid sociosexual adjustment may serve to predispose a schizophrenic individual to manifest characteristics of the "deficit" syndrome (48) found in the most severely deteriorated patients. These data raise the question of whether the chronicity and overall psychopathology of these patients are a result of the greater number of risk factors they manifest and whether additional risk factors may be present. Little is known about possible biological and psychophysiological factors associated with poor premorbid social functioning and later severe social deterioration in schizophrenic patients. Such information could help to identify additional risk factors in vulnerable individuals.

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DSM-III Disorders in a Large Sample of Psychiatric Patients: Frequency and Specificity of Diagnoses

Juan E. Mezzich, M.D., Ph.D., Horacio Fabrega, Jr., M.D.,
Gerald A. Coffman, M.S., and Rita Haley, M.S.

This study examined certain nosological features of DSM-III axis I diagnostic categories and subcategories as applied to 11,292 general psychiatric patients presenting for care, using a semistructured assessment procedure. The most frequently used major categories were affective, substance use, childhood-onset, and adjustment disorders. Secondary diagnoses were given to 26% of the patients. Male patients predominated in the categories of impulse-control, psychosexual, and substance use disorders, and female patients predominated in the categories of anxiety, affective, and somatoform disorders. Of the 329 five-digit subcategories available in DSM-III, 296 (90%) were actually used. Sixteen percent of the patients were given unspecific primary diagnoses.

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Diagnosis has a central role in the clinical science of psychiatry; it defines the boundaries of the field and its internal structure. As noted by Feinstein (1), diagnostic categories provide the locations where clinicians store the observations of professional experience, and the diagnostic taxonomy embodies the patterns according to which clinicians observe, think, remember, and act. The diagnostic enterprise is currently articulated to a large extent by *DSM-III* (2), not only in the United States but in many other parts of the world as well (3).

The innovative nature of *DSM-III* demands empirical appraisal of its clinical applicability and use. The categories that reference psychiatric disorders consti-

tute central descriptors of clinical conditions in either uniaxial or multiaxial systems, and the way these categories are used deserves particular attention. The frequency of use of diagnostic categories, computed for a total clinical or community sample, as well as for key demographic groups within the sample, is important to know, because it provides a psychopathology profile of the corresponding population.

Appraisal of *DSM-III* diagnostic patterns can be conducted in both community and clinical settings. The former is the natural matrix for examining samples of individuals experiencing certain pathological manifestations, regardless of the treatment received. Community studies typically yield substantial information on common disorders only and are not entirely free of sample representation problems. On the other hand, studies of clinical populations are affected by patients' help-seeking attitudes and various barriers to care, but such studies are crucial for determining how major diagnostic categories and their subcategories are actually used. Most of the systematic diagnostic studies in such settings reported to date have dealt only with selected conditions, for example, syndromes presented by students at a university clinic (4).

The present study was aimed at determining certain structural features of *DSM-III* axis I diagnosis as applied to all new patients presenting for care at a large, comprehensive psychiatric facility during a 4-year period. It is noteworthy that this sample was composed of patients who, upon completion of their evaluations, were assigned to either inpatient (the setting for most clinical reports) or outpatient care. Patients were evaluated by a primary clinician and a senior psychiatrist by means of a standardized procedure that uses all sources of information available and allows the use of all diagnostic categories in *DSM-III*. Specific questions investigated and reported here include the frequency with which the various categories and subcategories of *DSM-III* psychiatric syndromes were used as primary, secondary, third, and fourth diagnoses; diagnostic profiles of the patients, grouped by age and sex; and the degree of coverage of this large general psychiatric sample by specific diagnostic categories as contrasted to undefined ones. Questions relevant to comorbidity patterns are discussed elsewhere (5).

Received Feb. 4, 1988; revision received July 13, 1988; accepted Aug. 18, 1988. From the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Mezzich, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

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METHOD

The settings for this study were the Diagnostic Evaluation Center, a 24-hours-a-day, 7-days-a-week walk-in clinic, and the assessment components of clinical modules, all at the Western Psychiatric Institute and Clinic in Pittsburgh, Pa. These units conduct the initial comprehensive evaluations of all patients presenting for care before clinical dispositions (inpatient or outpatient treatment or no care needed) are made. Western Psychiatric Institute and Clinic is a large, comprehensive, urban university psychiatric facility that also serves as a community mental health center. It admits approximately 2,000 inpatients a year and has more than 100,000 outpatient visits a year. This clinic population includes persons of all ages who experience a wide diversity of forms and levels of psychopathology. It is served through specialized child, adolescent, adult, and geriatric treatment programs.

Patients' evaluations are typically conducted by a team composed of a primary clinician (a resident, medical student, mental health professional trainee, or nurse clinician specially trained in psychiatric assessment) and a senior psychiatrist. The primary clinician reviews available past records and any documents presented at the time of the interview, interviews the patient and persons who accompany him or her, and, if appropriate, makes telephone contact with relatives and health professionals. The clinician then presents the case to the psychiatrist, who conducts a brief complementary interview of the patient and the accompanying persons to clarify diagnostic formulation and dispositional issues. Finally, clinical and legal dispositions are made jointly by the primary clinician and the psychiatrist.

The assessment process is conducted according to the guidelines of the Initial Evaluation Form (6), a standardized instrument that specifies and defines the items to be covered and allows the clinician the flexibility to adjust the order of items in the interview and probe for information as needed. Information is obtained from all available living informants and documentary sources. The sections of the form include history of present illness; symptom inventory; family, personal, and social histories; physical health history and examination; diagnostic formulation; and disposition. The recording format includes narrative and structured components that complement one another.

The Initial Evaluation Form was designed to cover all psychiatric disorders and is keyed to *DSM-III* criterion markers. The diagnostic format provides space and guidelines for statements along all axes of the *DSM-III* system. For axis I, which is the subject of the present study, slots are provided for up to four main formulation diagnoses. In accordance with *DSM-III* guidelines, clinicians are encouraged to specify as many diagnoses as appropriate for describing the patient's condition and to rank them according to importance for evaluation and care. There is also space

for up to four alternative or additional diagnostic possibilities.

Completed Initial Evaluation Forms are regularly checked by an administrative clinician, and their structured components are computerized as part of our institution's clinical information system (7, 8). The resulting database is being used to answer a number of patient care and research questions, such as the relationship between symptoms and outpatient versus inpatient dispositions (9). The form is also used in other facilities, allowing regional and international comparative studies (10).

The subjects of this study consisted of the 11,292 new patients who presented for care at the Western Psychiatric Institute and Clinic from August 1980 through December 1984. This count does not include any duplications, since patients who received more than one evaluation during the study period were considered only once. Upon completion of the Initial Evaluation Form, 36% were admitted to inpatient care, 34% were referred to our outpatient clinics, and 30% were referred to other health facilities or social agencies.

Of the 11,292 study patients, 17% were 18 years of age or younger, 73% were 19–59 years old, and 10% were 60 years of age or older. Fifty-four percent were female and 46% were male. Fifty percent of the patients had never been married, 26% were married, 7% were separated, 11% were divorced, and 5% were widowed. The ethnic composition of the group was 74% white, 25% black, and 1% other. With respect to religion, 37% of the patients were Protestant, 36% were Catholic, 6% were Jewish, 9% reported other religious affiliations, and 11% reported no affiliation. Social class designations according to the Hollingshead scale (11) placed 13% of the patients in class I (the highest), 11% in class II, 9% in class III, 23% in class IV, and 44% in class V (the lowest).

RESULTS

The rates of axis I major psychiatric syndrome categories used as primary, secondary, third, and fourth diagnoses for all 11,292 of the general psychiatric patients were analyzed first; these are presented in table 1. (A table containing detailed diagnostic categories and subcategories is available on request.) All rates refer to current diagnoses. Positive primary diagnoses were made for 90% of the patients (7% had diagnosis deferred, and for about 3% no diagnosis was given on this axis). A second diagnosis in the main formulation was made for 26% of the patients, a third for 6%, and a fourth for 1%.

In the primary diagnosis position, all *DSM-III* major categories of mental disorders were used, although with wide variation in frequency rates. The major category most frequently used as a primary diagnosis was affective disorders (33%), and within these, major depression predominated (23%). Next came adjustment

TABLE 1. Rates of *DSM-III* Axis I Major Categories Used as Primary, Secondary, Third, and Fourth Diagnoses for 11,292 General Psychiatric Patients

Major Diagnostic Category	Diagnosis							
	Primary		Secondary		Third		Fourth	
	N	%	N	%	N	%	N	%
Disorders usually first evident in infancy, childhood, or adolescence	1,100	9.7	541	4.8	134	2.2	22	0.2
Organic mental disorders	631	5.6	130	1.2	41	0.4	4	0.0
Substance use disorders	932	8.3	1,175	10.4	263	2.3	41	0.4
Schizophrenic disorders	821	7.3	25	0.2	0	0.0	0	0.0
Paranoid disorders	63	0.6	1	0.0	1	0.0	0	0.0
Psychotic disorders not elsewhere classified	472	4.2	24	0.2	4	0.0	0	0.0
Affective disorders	3,694	32.7	326	2.9	24	0.2	5	0.0
Anxiety disorders	769	6.8	112	1.0	15	0.1	2	0.0
Somatoform disorders	40	0.4	19	0.2	2	0.0	0	0.0
Dissociative disorders	7	0.1	5	0.0	1	0.0	0	0.0
Psychosexual disorders	55	0.5	41	0.4	8	0.1	0	0.0
Factitious disorders	3	0.0	1	0.0	0	0.0	0	0.0
Disorders of impulse control not elsewhere classified	50	0.4	17	0.2	7	0.1	1	0.0
Adjustment disorder	1,117	9.9	104	0.9	14	0.1	2	0.0
Psychological factors affecting physical condition	43	0.4	10	0.1	4	0.0	0	0.0
Unspecified mental disorder (nonpsychotic)	35	0.3	2	0.0	1	0.0	1	0.0
Conditions not attributable to a mental disorder (V codes)	313	2.8	398	3.5	126	1.1	27	0.2
Diagnosis deferred	834	7.4						
No diagnosis	313	2.8	8,361	74.1	10,647	94.3	11,187	99.0

disorder (10%), particularly that with depressed mood (5%); disorders usually starting in childhood or adolescence (10%), especially conduct disorders (3%); substance use disorders (8%), among which predominated alcohol abuse or dependence (5%); schizophrenic disorders (7%), the paranoid subtype being the most frequent (4%); and anxiety disorders (7%), half of these corresponding to phobias.

In the secondary diagnosis position, the most frequent category by far was substance use disorders (10%), accounting for 40% of the positive diagnoses made in this position; alcohol abuse was the predominant subcategory. Next came disorders usually starting in childhood or adolescence (5%) (mental retardation was most prominent, at a rate of 2%) and conditions not attributable to a mental disorder, or V codes (4%) (marital problems and parent-child problems accounted together for half of the cases in this and all other diagnostic positions). Further, it is noteworthy that substance use disorders, mental retardation, and conditions not attributable to a mental disorder were more frequent as secondary than as primary diagnoses.

Ranking patterns similar to those for secondary diagnoses were found for diagnoses in the third and fourth positions of the axis I diagnostic formulation. The most frequently used major category in these positions was substance use disorders, but in contrast to the subcategory findings in the first and second positions, other, mixed, or unspecified substance abuse was predominant. Next came disorders usually starting in childhood or adolescence (mental retardation was the predominant subcategory) and V code conditions.

In our analysis of the frequency of use of the diagnostic categories regardless of position within the main formulation for axis I, the following categories attained the highest frequencies: affective disorders (35%), substance use disorders (17%), disorders usually starting in childhood or adolescence (12%), adjustment disorder (11%), anxiety disorders (8%), schizophrenic disorders (7%), organic mental disorders (7%), and conditions not attributable to a mental disorder (7%). The major contrasts with the primary diagnosis findings were in the category of substance use disorders, which moved from fourth place as a primary diagnosis (8%) to second place in overall frequency (17%), and in conditions not attributable to a mental disorder, which increased from 3% as a primary diagnosis to 7% in overall frequency. These changes reflect the previously noted prominence of substance use disorders and V code conditions as secondary, third, and fourth diagnoses (a similar prominence was attained by the mental retardation subcategory of disorders usually starting in childhood or adolescence).

The rates of axis I major diagnostic categories in three age groups (child/adolescent, adult, and elderly) are displayed in table 2. The data show the patients in each age group who received each axis I diagnosis in one or more of the four diagnostic positions.

Among children and adolescents (18 years old or younger), all major diagnostic categories except factitious disorders were represented. The most frequent categories were disorders usually starting in childhood or adolescence (60%), adjustment disorder (16%), affective disorders (13%), and V code conditions (13%). It should be pointed out that disorders usually starting

TABLE 2. Rates of DSM-III Axis I Major Diagnostic Categories^a Used for Child/Adolescent, Adult, and Elderly Psychiatric Patients^b

Major Diagnostic Category	Age 18 Years or Younger (N=1,868)		Age 19–59 Years (N=8,242)		Age 60 Years or Older (N=1,157)	
	N	%	N	%	N	%
Disorders usually first evident in infancy, childhood, or adolescence	1,124	60.2	248	3.0	11	1.0
Organic mental disorders	98	5.2	345	4.2	358	30.9
Substance use disorders	113	6.0	1,729	21.0	81	7.0
Schizophrenic disorders	24	1.3	767	9.3	50	4.3
Paranoid disorders	1	0.1	51	0.6	13	1.1
Psychotic disorders not elsewhere classified	56	3.0	411	5.0	30	2.6
Affective disorders	248	13.3	3,110	37.7	540	46.7
Anxiety disorders	29	1.6	781	9.5	51	4.4
Somatoform disorders	3	0.2	41	0.5	8	0.7
Dissociative disorders	2	0.1	10	0.1	1	0.1
Psychosexual disorders	11	0.6	84	1.0	2	0.2
Factitious disorders	0	0.0	4	0.0	0	0.0
Disorders of impulse control not elsewhere classified	22	1.2	53	0.6	0	0.0
Adjustment disorder	304	16.3	894	10.8	24	2.9
Other psychiatric disorders ^c	10	0.5	77	0.9	7	0.6
Conditions not attributable to a mental disorder (V codes)	246	13.2	513	6.2	26	2.2
Diagnosis deferred	107	5.7	662	8.0	77	6.7
No diagnosis	39	2.1	236	2.9	7	0.6

^aUsed as primary, secondary, third, and fourth diagnoses on axis I.^bData on about 25 cases are missing.^cA combination of "psychological factors affecting physical condition" and "unspecified mental disorder (nonpsychotic)."

in childhood or adolescence do not include all diagnoses that can be used for children and adolescents; patients in this age group can be given diagnoses in most of the other major diagnostic categories, such as schizophrenic, affective, and adjustment disorders.

The diagnostic profile of the adult group (19–59 years of age) covered all major categories without exception. The most frequent were affective disorders (38%), substance use disorders (21%), adjustment disorder (11%), anxiety disorders (9%), and schizophrenic disorders (9%). Adult patients may also be given current diagnoses of a variety of disorders that usually start in childhood or adolescence (such as mental retardation and anorexia nervosa), although this does not happen very frequently.

The oldest group (60 years of age or older) had diagnoses in a wide range of axis I major diagnostic categories, the only exceptions being factitious disorders and impulse-control disorders not classified elsewhere. At the high-frequency end of the profile were affective (47%) and organic mental (31%) disorders.

Diagnostic profiles based on gender are shown in table 3. Among females presenting for care, the most frequent major category (listed as primary, secondary, third, and fourth diagnoses on axis I) was affective disorders (41%), followed at a distance by substance use disorders (12%), adjustment disorder (12%), and anxiety disorders (10%). Among males, the most frequent major diagnostic categories were affective disorders (27%), substance use disorders (23%), disorders usually starting in childhood or adolescence (17%), and schizophrenic disorders (10%).

Also of interest are the female/male and male/female ratios adjusted for overall gender rates, i.e., corrected for the imbalance between females (54%) and males (46%) in the total sample presenting for care. The greatest female/male ratios were obtained for anxiety disorders (1.71), affective disorders (1.53), and somatoform disorders (1.49). On the other hand, the greatest male/female ratios were for impulse-control disorders not elsewhere classified (6.67), psychosexual disorders (5.88), substance use disorders (2.00), disorders usually starting in childhood or adolescence (1.92), and schizophrenic disorders (1.75).

DSM-III (pp. 15–19) includes 329 diagnostic subcategories on axis I, including those resulting from fifth-digit specifications. The number of such subcategories used for diagnosis of the 11,292 persons seeking care at our comprehensive psychiatric institute was 296, or 90% of all the available diagnoses.

The most frequent five-digit subcategories were major depression, recurrent, without melancholia (7.4%); major depression, single episode, unspecified subtype (6.6%); dysthymic disorder (6.2%); adjustment disorder with depressed mood (5.8%); atypical psychosis (2.8%); adjustment disorder with mixed emotional features (2.5%); agoraphobia with panic attacks (2.3%); and schizophrenia, paranoid, chronic (2.2%).

Table 4 presents the numbers of subcategories within each major category on axis I that were actually used. For seven of the 17 positive major diagnostic categories, all of the available five-digit subcategories were used. For the remaining 10 major categories, be-

TABLE 3. Rates of DSM-III Axis I Major Diagnostic Categories^a Used for Female and Male Psychiatric Patients^b

Major Diagnostic Category	Female (N=6,071)		Male (N=5,215)		Female/Male Ratio ^c
	N	%	N	%	
Disorders usually first evident in infancy, childhood, or adolescence	524	8.6	860	16.5	0.52
Organic mental disorders	400	6.6	407	7.9	0.84
Substance use disorders	707	11.6	1,218	23.4	0.50
Schizophrenic disorders	336	5.5	509	9.8	0.57
Paranoid disorders	34	0.6	31	0.6	0.94
Psychotic disorders not elsewhere classified	246	4.1	251	4.8	0.84
Affective disorders	2,501	41.2	1,400	26.8	1.53
Anxiety disorders	574	9.5	288	5.5	1.71
Somatoform disorders	33	0.5	19	0.4	1.49
Dissociative disorders	13	0.2	0	0.0	
Psychosexual disorders	16	0.3	81	1.6	0.17
Factitious disorders	2	0.0	2	0.0	0.86
Disorders of impulse control not elsewhere classified	11	0.2	64	1.2	0.15
Adjustment disorder	738	12.2	497	9.5	1.28
Other psychiatric disorders ^d	58	1.0	36	0.7	1.38
Conditions not attributable to a mental condition (V codes)	404	6.7	381	7.3	0.91
Diagnosis deferred	443	7.3	391	7.5	0.97
No diagnosis	174	2.9	139	2.7	1.08

^aUsed as primary, secondary, third, and fourth diagnoses on axis I.^bIn six cases the gender of the patient was not recorded.^cEach ratio was adjusted for overall gender rates, e.g., female/male ratio for the first category = $(524 \times 5,215) / (860 \times 6,071)$.^dA combination of "psychological factors affecting physical condition" and "unspecified mental disorder (nonpsychotic)."

TABLE 4. Diagnostic Subcategories Used for 11,292 General Psychiatric Patients and Subcategories Available in Each DSM-III Axis I Major Category

Major Diagnostic Category	Subcategories		Percent of Available Subcategories Used
	Number Used	Number Available	
Disorders usually first evident in infancy, childhood, or adolescence	45	47	95.7
Organic mental disorders	51	61	83.6
Substance use disorders	65	72	90.3
Schizophrenic disorders	27	30	90.0
Paranoid disorders	3	4	75.0
Psychotic disorders not elsewhere classified	4	4	100.0
Affective disorders	31	32	96.9
Anxiety disorders	10	10	100.0
Somatoform disorders	5	5	100.0
Dissociative disorders	3	5	60.0
Psychosexual disorders	20	25	80.0
Factitious disorders	2	3	66.7
Disorders of impulse control not elsewhere classified	5	6	83.3
Adjustment disorder	8	8	100.0
Psychological factors affecting physical condition	1	1	100.0
Unspecified mental disorder (nonpsychotic)	1	1	100.0
Conditions not attributable to a mental disorder (V codes)	13	13	100.0
Diagnosis deferred	1	1	100.0
No diagnosis	1	1	100.0
Total	296	329	90.0

tween 60% and 97% of the available subcategories were used.

Among the disorders usually starting in childhood or adolescence, the diagnoses of rumination disorder of infancy and transient tic disorder were not applied. With respect to organic mental disorders, the only problematic area was that of organic mental disorders

induced by substances other than alcohol, where nine of the 31 subcategories available were not used, including amnesic and dementia syndromes induced by nonalcoholic substances.

In the category of substance use disorders, all subcategories related to alcohol were used. All of those related to other substances were applied when the

fifth digit indicating episode subtype was ignored, but when these subtypes were considered, seven of the 60 subtypes turned out to have been unused. All of these subtypes referred to dependency on four drugs, particularly when the course of the disorder was episodic. Among the schizophrenic disorders, all five symptom types were represented. All of the subtypes according to course were covered except disorganized, in remission, and catatonic, subchronic and in remission. Among the four paranoid disorders, only shared paranoid disorder was not used.

In the affective disorders category, the only subcategory not used, out of the 32 available, was bipolar disorder, depressed, with mood-incongruent psychotic features. Among the dissociative disorders, which in general were used infrequently, two of the subcategories (psychogenic fugue and multiple personality) were not used at all. In the psychosexual disorders category, five of the 25 available subcategories were not applied; these included transsexualism with heterosexual history, gender identity disorder of childhood, zoophilia, functional dyspareunia, and functional vaginismus. Among the factitious disorders, the only one of the three subcategories that was not used was atypical factitious disorder with physical symptoms. Among the six subcategories of impulse-control disorders not elsewhere classified, only kleptomania was not represented.

The final issue we explored was the extent to which the patients presenting for psychiatric care were included in specific versus unspecific categories on axis I. An appraisal of the magnitude of the lack of diagnostic specificity is presented in table 5, which displays a frequency analysis of primary diagnoses that were in the atypical or undefined subcategories within each major category on axis I.

Of course, all cases of unspecified (nonpsychotic) mental disorder and of deferred diagnosis were considered unspecific. The most problematic differentiated diagnostic category was psychotic disorders not elsewhere classified, as 63% of the diagnoses in this category were in the atypical psychosis subcategory (the use of which primarily referred to a psychosis of a type that could not be specified at the time rather than to an exotic psychosis). A similar percentage (57%) of the patients with primary diagnoses of dissociative disorders were placed in the atypical subcategory. Across diagnostic categories, 16% of the 11,292 individuals presenting for psychiatric care received primary atypical or undefined diagnoses on axis I.

DISCUSSION

The first set of findings involved the rate of use of diagnostic categories. It was documented that all 17 major categories of mental disorders on axis I (i.e., the major classes printed in bold letters in *DSM-III*) were used, although with widely diverse frequencies. In the literature, the few reports on rates of diagnoses for large samples in which the disorders were formulated

TABLE 5. Primary Unspecific (Atypical or Undefined) Diagnoses in Each *DSM-III* Axis I Major Category Used for 11,292 General Psychiatric Patients

Major Diagnostic Category	Number of Primary Diagnoses	Unspecific Diagnoses	
		N	%
Disorders usually first evident in infancy, childhood, or adolescence	1,100	69	6.3
Organic mental disorders	631	106	16.8
Substance use disorders	932	197	21.1
Schizophrenic disorders	821	0	0.0
Paranoid disorders	63	10	15.9
Psychotic disorders not elsewhere classified	472	295	62.5
Affective disorders	3,694	169	4.6
Anxiety disorders	769	55	7.2
Somatoform disorders	40	4	10.0
Dissociative disorders	7	4	57.1
Psychosexual disorders	55	11	20.0
Factitious disorders	3	0	0.0
Disorders of impulse control not elsewhere classified	50	11	22.0
Adjustment disorder	1,117	20	1.8
Psychological factors affecting physical condition	43	0	0.0
Unspecified mental disorder (nonpsychotic)	35	35	100.0
Conditions not attributable to a mental disorder (V codes)	313	0	0.0
Diagnosis deferred	834	834	100.0
No diagnosis	313		
Total	11,292	1,820	16.1

according to *DSM-III* or a similar diagnostic system have been from community surveys. Weissman et al. (12), using the Schedule for Affective Disorders and Schizophrenia (13) to study the rates of a set of psychiatric disorders in a Connecticut urban community, found that the most frequent ones were major depression and alcohol dependence. More recently, Robins et al. (14), using the NIMH Diagnostic Interview Schedule (DIS) (15) to investigate the lifetime prevalence in three catchment areas of the 15 *DSM-III* diagnoses covered by the DIS, reported that the most frequent disorders were alcohol abuse/dependence, phobias, major depression, and drug abuse/dependence. On the basis of the same evaluation instrument and catchment areas, Myers et al. (16) reported that, in terms of 6-month prevalence, the most frequent DIS/*DSM-III* diagnoses were phobias, alcohol abuse/dependence, dysthymic disorder, and major depression.

To offer a comparative view of community and clinical sample diagnostic rankings, table 6 displays frequency figures for the 11 *DSM-III* axis I diagnoses considered in the Myers et al. study (16) and the figures we obtained for the corresponding diagnoses in the present clinical study—in both cases, for patients 18 years of age or older. For seven of the 11 diagnoses, the frequency rankings in the two samples were identical or within two steps. The greatest discrepancy was in phobias, which achieved the highest ranking in the community sample but was in the bottom half in the

TABLE 6. Distribution of 11 *DSM-III* Axis I Diagnoses Used for Patients 18 Years of Age or Older in a Community Sample and in the Present Study

Diagnosis	Community Sample (16) (N=9,543)		Clinical Sample (Present Study) (N=9,594)	
	%	Rank	%	Rank
Alcohol abuse/dependence	5.03	2	12.73	2
Other substance abuse/dependence	2.01	5	9.76	3
Schizophrenia	0.91	7	8.48	4
Schizophreniform disorder	0.14	10	0.53	10
Manic episode	0.62	9	2.25	7
Major depression	2.96	4	26.34	1
Dysthymic disorder	2.99	3	6.43	5
Phobias	8.48	1	4.46	6
Panic disorder	0.84	8	1.09	8
Obsessive-compulsive disorder	1.58	6	1.06	9
Somatization disorder	0.10	11	0.22	11

clinical sample. It seems reasonable to view this discrepancy as related to selection factors. Phobias usually produce intermittent pain/disability, and individuals with these complaints probably enjoy a relatively better level of adaptive functioning than those with other psychiatric disorders, whose pain/disability is more continuous. Moreover, in some cases, phobic individuals may have fears of doctors or of leaving home, which would reduce the likelihood of their requesting psychiatric treatment. Finally, it is possible that the discrepancy develops because patients seeking professional care have more severe phobias, whereas individuals in community surveys have less clinically significant phobias. Next in divergence was obsessive-compulsive disorder, which was ranked sixth in the community sample but only ninth in the clinical study. Also in this case, selection factors related to adaptive functioning appear to be a plausible explanation. The other two noticeable discrepancies were in major depression and schizophrenia; the higher ranking of these diagnoses in the clinical sample than in the community sample may be related to their levels of psychopathological and social dysfunction and to preferential referral patterns.

Among the secondary, third, and fourth axis I diagnoses given to 26% of the patients in our study, the most prominent were substance use disorders, mental retardation, and conditions not attributable to a mental disorder (V codes), which also turned out to be more frequent as secondary than as primary diagnoses. From a multiaxial viewpoint, this may suggest that these diagnoses could be placed on a separate axis. In fact, mental retardation has been moved to axis II in *DSM-III-R*. Substance abuse is considered on a separate axis dealing with "associated factors" in the first multiaxial diagnostic system proposed in the United States for general psychiatric patients (17), and this certainly would be worth considering in any multiaxial system designed specifically for patients likely to have substance use disorders (who often have an additional

psychiatric disorder). V code conditions, which for the most part arise from abnormal psychosocial situations or stress-related incidents, have been shown to contrast thoroughly with even the marginal or transitional categories of axis I, such as adjustment disorder (18). The V codes have two roles in *DSM-III*: one is to justify or explain the contact with the health care system of an individual who is not ill, and the other is to point out the presence of a psychosocial situation that must be taken into account in patient care. The fact that such conditions appeared more often as secondary than as primary diagnoses suggests that they are predominantly used to specify psychosocial situations relevant to patient care. In a fully implemented multiaxial formulation, this specifying role could be better handled by extending the scope of *DSM-III* axis IV to include not only an overall severity rating but also a listing of specific psychosocial situations or stressors that may merit clinical intervention and further evaluation.

Another set of our findings dealt with diagnostic profiles for broad age and gender groups. In line with the high frequency of affective and organic mental disorders in the elderly patients in our study, Myers et al. (16) reported cognitive impairment, phobias, dysthymic disorder, and major depression as the most frequent DIS/*DSM-III* diagnoses among the elderly individuals surveyed in three communities. The discrepancy in frequency of phobias between the Myers et al. study and ours might be explained along the lines we have already discussed.

The gender distribution of our general psychiatric sample (54% female and 46% male) has a striking similarity to international findings. For example, in a clinical census study covering inpatients, outpatients, and day hospital patients in Denmark, Kastrup (19) reported that 56% were female and 44% were male. A recent study of treated mental disorders in Upper Bavaria, Federal Republic of Germany, conducted by Dilling and Weyerer (20), which also covered inpatients and outpatients, showed that 54% of the patients were female and 46% were male. In the previously mentioned studies that surveyed three communities with the DIS (14, 16), 60% of the individuals with DIS/*DSM-III* diagnoses were female and 40% were male.

The predominance of males with diagnoses of substance use disorders, which we found in the present study, has been widely recognized in both clinical (19, 20) and community (14, 16) studies. Our finding of a predominance of males with disorders usually starting in childhood or adolescence is in accord with the results of a study of the community prevalence of *DSM-III* disorders in preadolescent children in Dunedin, New Zealand (21), which found a 1.7 ratio of boys to girls. In keeping with the slight predominance of males with diagnoses of schizophrenia in our study, a similar finding was obtained in a national clinical sample by Kastrup (19); however, this ratio was found to vary across age groups and sites in the Myers et al. community study (16). For the strong preponderance of

males observed in the present study in the categories of impulse-control disorders and psychosexual disorders, no adequate comparison data were found in the literature, probably because most systematic *DSM-III* studies have used instruments such as the DIS, which do not cover the relevant *DSM-III* categories. The predominance of females with anxiety, affective, and somatoform disorders that we found in our study is quite in line with both clinical and community reports. For example, in a treated sample, Kastrup (19) found that neurotic disorders were twice as frequent in females as in males, and Dilling and Weyerer (20) reported that affective and neurotic/psychosomatic illnesses were overrepresented in females. The previously noted community studies (14, 16) found a predominance of females with such affective disorders as major depression and dysthymia; anxiety disorders such as phobic, panic, and obsessive-compulsive disorders; and somatization disorder.

With respect to the use of subcategories, including the five-digit ones, we found that some of these (particularly within the organic mental, psychosexual, and dissociative disorders categories) were not used at all for the 11,292 general psychiatric patients in our study. Besides indicating obvious selection factors (as reviewed earlier), the finding of unused subcategories may indicate that some conditions are highly infrequent in contemporary U.S. society (e.g., multiple personality) or in urban areas (e.g., zoophilia), while other conditions (e.g., functional dyspareunia) may occur as part of more encompassing syndromes (e.g., somatization disorder). The scarcity of reports on subcategories in the literature may reflect the limitations of community studies and fully structured diagnostic instruments in identifying uncommon cases.

The 16% overall rate of unspecific, atypical, and deferred diagnoses found in the present study may not appear unduly large, but it is not trivial or negligible. It reflects limitations in the development of a fully specified diagnostic tool purported to be explicit or operational in its definitions. The absence of literature reports in this area may also be attributed to the factors outlined before with respect to diagnostic subcategories.

We suggest that future researchers implement community studies by using new evaluation instruments which cover all *DSM-III* disorders and that studies of clinical samples use procedures which ensure reasonable rigor in the evaluation of patients while allowing adequate coverage of the whole domain of psychopathology.

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Hierarchy of Characteristics Associated With Depressive Symptoms in an Urban Elderly Sample

Gary J. Kennedy, M.D., Howard R. Kelman, Ph.D., Cynthia Thomas, Ph.D.,
Wendy Wisniewski, M.A., M.Ed., Helen Metz, Ph.D., and Polly E. Bijur, Ph.D.

In contrast to the uncertainty about the prevalence and importance of late-life depressive disorders, a consistent pattern of risk factors for depressive symptoms has been shown by studies using the Center for Epidemiologic Studies Depression Scale (CES-D). The authors surveyed a representative sample of 2,137 elderly community residents with the CES-D and found a hierarchy of characteristics associated with substantial levels of depressive symptoms: illness, disability, isolation, bereavement, and poverty. If these findings are confirmed by prospective studies, addressing modifiable factors in the emergence, persistence, and remission of depressive symptoms might extend the independent survival of older adults.

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The current understanding of late-life depression might best be described by the following paradox: although the prevalence of depressive symptoms increases with age, the prevalence of major depressive disorders does not. The paradox arises in part from a tendency to conceptualize depression three ways at once, i.e., as a mood, as an illness, and as a state best characterized by functional disability (1). Recent studies have highlighted rather than resolved this paradox. The Epidemiologic Catchment Area Program studies were sponsored to provide geographically comparable rates of mental disorders (2). However, the contrast between the resulting low prevalence of depressive disorders, roughly 2% or less (3), and the presence of depressive symptoms in more than 20% of the respondents (1) caused considerable controversy. In the Epidemiologic Catchment Area Program studies, a

nonclinician interviewer completes the Diagnostic Interview Schedule (DIS) (4), which was derived from DSM-III. Kermis (5) argued that this method has led to an underestimate of depression and an overestimate of dementia in aged persons in the community. The DIS assesses only major episodes of depression; it excludes minor episodes, bereavement, and depressive symptoms associated with physical illness. This focus on the identification of major mental disorders is reasonable for younger groups, in which a single diagnostic entity is likely to be the major determinant of impaired function, but not for the elderly, in whom bereavement, symptoms of minor depression, and multiple somatic conditions interact in life-threatening ways (6, 7).

In contrast to the uncertainty over the prevalence and importance of major depressive syndromes in the elderly, studies (8-13) using the Center for Epidemiologic Studies Depression Scale (CES-D) (14) have demonstrated a consistent pattern of risk factors for depressive symptoms. Studies of heterogeneous samples indicate that poor health, bereavement, lack of companionship, female gender, economic deprivation, and, to a lesser extent, age are associated with the expression of substantial levels of depressive symptoms. The importance of these findings is obscured by the lack of information about their impact on the survival and functional independence of older adults in the community, a problem made more obvious by the Epidemiological Catchment Area Program studies. This is particularly important for dementia and depression, in which early identification before full expression of the disorder could significantly extend independent survival in the community.

With these issues in mind we focused on cross-sectional characteristics—their hierarchy and relative risk in relation to depressive symptoms—that emerged from interviews of individuals aged 65 and older in an urban community. Our cross-sectional analysis sets the stage for the longitudinal identification of characteristics that modulate the expression of depressive symptoms and might be targets for intervention.

METHOD

Study subjects were selected from a list of the addresses of Medicare recipients living in the study area

Received Dec. 22, 1987; revised June 20, 1988; accepted Aug. 31, 1988. From the Division of Geriatric Psychiatry, Department of Psychiatry, and the Division of Health Services Organization and Policy, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, New York, Montefiore Medical Center, and Bronx Psychiatric Center, Bronx, N.Y. Address reprint requests to Dr. Kennedy, Division of Geriatric Psychiatry, Montefiore Medical Center, 111 East 210th St., Bronx, NY 10467.

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and from lists of individuals not enrolled in Medicare. Of the 2,576 randomly selected households, 1,855 (72%) agreed to join the study (15). When weighted for the actual number of older adults per household in the study area, the sample represents an estimated 2,137 individuals, and analyses were based on this latter figure. Between 1984 and 1985 the respondents provided extensive information on health, physical and social functioning, utilization of and attitudes toward health care, financial resources, and interactions with family and friends. They were also queried with the CES-D and Mini-Mental State (16), and the conventional CES-D cutoff point of 16 was used to designate respondents as depressed (11–14, 17, 18). It is important to note that, in referring to respondents as depressed, we are referring to symptoms of depression rather than a clinical diagnosis of depressive disorder.

Similarly, the Mini-Mental State is considered a screening instrument for cognitive impairment rather than a diagnostic indicator of dementia (16, 19, 20). It was originally constructed for bedside or clinic evaluation but has been modified for community administration. We further modified the Mini-Mental State by deleting one orientation question (city), combining day and month into a one-point answer, and transforming the registration score from a maximum of 3 points to a maximum of 1. We chose a cutoff score of 18 after inspecting the distribution of scores in our sample. Cronbach's alpha coefficient for our modified version of the Mini-Mental State was 0.63, indicating acceptable internal consistency for the modified instrument.

Chi-square tests were used to assess statistical associations between the CES-D score and categorical variables, such as gender. For characteristics such as age, which have quantitatively ordered categories, Mantel-Haenszel chi-square tests for linear trends were employed. To better understand the relative magnitude of the relationships between variables, we calculated odds ratios as estimates of relative risk and performed multiple regression analyses using sets of variables grouped on the basis of their potential for intervention. A significance criterion of 0.01 was employed in all analyses. Analyses were performed with Statistical Analysis Systems programs (21).

RESULTS

Sociodemographic Variables

With the CES-D cutoff score of 16, it was determined that substantial levels of depressive symptoms were present in 16.89% of the sample—11.14% of the men and 19.91% of the women. When the sample was stratified by age and gender, we found that depression was associated with age in women (Mantel-Haenszel $\chi^2=15.80$, $df=2$, $p=0.0001$) but not in men (Mantel-Haenszel $\chi^2=2.26$, $df=2$, $n.s.$). The relationship between income and depression was highly significant

(Mantel-Haenszel $\chi^2=18.58$, $df=1$, $p=0.0001$) and was an inverse relationship—as income increased the prevalence of depression decreased, as shown in table 1. Education was significantly related (Mantel-Haenszel $\chi^2=6.02$, $df=1$, $p=0.014$), but the relative risk value was modest. In contrast, the size of the relationship was much larger for religious identification; the prevalence of depressive symptoms among respondents identifying themselves as Jewish was twice that found among Catholics.

As expected, the prevalence of depression was considerably greater among respondents with fewer opportunities for companionship, including widows and those who lived alone, spent the day alone, had no one in whom to confide, were not employed, or did not make new friends. With the exception of employment, the relative risk values were small. Bereavement is an obvious reason to express symptoms of depression, as is serious illness in a family member, and these relationships are reflected in our data. In contrast, depressive symptoms were no more prevalent among those who had lost close friends than among those who had not.

Health, Sleep Disturbance, and Cognitive Performance

As shown in table 2, the prevalence and relative risk of depressive symptoms were significantly related to number of medical conditions, number of problems in activities of daily living, variables indicating disability, perceived health, and number of visits to physicians. Those who perceived little control over their health and those who assessed their health as poor had high frequencies of depression, 30.61% and 54.01%, respectively. It is important to note that while only 11.15% of our respondents characterized their health as poor, 27.66% perceived little or no control over their health and the relative risk for depression among the latter group was five times as high as that for the respondents who believed they had much control over their health.

We grouped impairments in sleep and cognitive performance together because both are considered criteria for major depressive disorder. The respondents who reported one episode of sleep disturbance in the 2 weeks before their interviews had a low prevalence of depressive symptoms. However, those with two or more nights of difficulty falling asleep, staying asleep, or waking too early had more than four times the risk of depression as respondents with no sleep disturbance.

We found 23.05% of the sample to be cognitively impaired, according to the Mini-Mental State, and, as with depression, more women than men scored in the impaired range ($\chi^2=4.58$, $df=1$, $p=0.03$). However, unlike symptoms of depression, cognitive impairment increased with age regardless of gender (Mantel-Haenszel $\chi^2=191.63$, $df=2$, $p=0.0001$). When tests of association between age, gender, cognitive impairment, and depression were examined, a significant relation-

TABLE 1. Sociodemographic Characteristics and Relative Risk of Depression in 2,137 Elderly Subjects in the Community

Characteristic	Number Responding	Depressed		Relative Risk	95% Confidence Bounds
		N	%		
Demographic status					
Age (years)					
65-74	1,070	151	14.11	1.000	
75-84	862	161	18.68	1.398	1.096-1.782
85 or older	205	49	23.90	1.936	1.345-2.789
Gender					
Male	736	82	11.14	1.000	
Female	1,401	279	19.91	1.977	1.518-2.567
Annual income					
More than \$15,000	251	22	8.76	1.000	
\$5,000-\$15,000	808	155	19.18	2.672	1.803-3.960
Less than \$5,000	230	52	22.61	3.314	2.099-5.233
Receives Medicaid					
No	1,817	210	15.52	1.000	
Yes	283	73	25.80	1.890	1.407-2.533
Education (years)					
9 or more	1,250	190	15.20	1.000	
8 or fewer	867	167	19.26	1.360	1.082-1.710
Religious identification					
Catholic	1,014	123	12.13	1.000	
Other	282	38	13.48	1.128	0.764-1.667
Jewish	833	198	23.77	2.266	1.770-2.901
Opportunities for companionship					
Marital status					
Married	877	106	12.09	1.000	
Never married	251	38	15.14	1.294	0.867-1.932
Separated/divorced	112	18	16.07	1.389	0.807-2.393
Widowed	895	106	22.23	2.074	1.604-2.682
Other household members					
Spouse	864	99	11.46	1.000	
Others	364	55	15.11	1.385	0.971-1.976
None	909	207	22.77	2.273	1.751-2.949
Spends day with someone					
Yes	1,365	188	13.77	1.000	
No	763	172	22.54	1.819	1.446-2.288
Has someone to confide in					
Yes	1,828	283	15.48	1.000	
No	296	75	25.34	1.850	1.383-2.475
Is employed					
Yes	234	13	5.56	1.000	
No	1,903	384	18.29	3.809	2.152-6.745
Makes new friends					
Yes	313	34	10.94	1.000	
No	1,726	313	18.13	1.806	1.286-2.536
Family illness and bereavement					
Family member ill in last 6 months					
No	1,644	233	14.17	1.000	
Yes	475	123	25.89	2.113	1.649-2.707
Family member died in last 6 months					
No	1,776	275	15.48	1.000	
Yes	341	81	23.75	1.698	1.283-2.248

ship between depression and cognitive impairment was found only among women aged 75-84 years ($\chi^2=4.741$, $df=1$, $p=0.03$). The relationship of age and depression to cognitive performance is more clearly demonstrated by the rather modest relative risk values obtained when the two older groups are referenced to the younger. However, the risk of reporting depressive symptoms among those who admitted to needing help with finances or forgetting to take medications or pay bills was more substantial.

Hierarchy of Characteristics Associated With Depressive Symptoms

Although the relationships presented in tables 1 and 2 are consistent with patterns observed by other investigators, in many cases the size of the relationships, as shown by the relative risk value, is small despite being highly significant. To better understand the hierarchy and magnitude of the various contributors to depression, we performed regression analyses of groups of

TABLE 2. Health, Sleep, Cognitive Performance, and Relative Risk of Depression in 2,137 Elderly Subjects in the Community

Characteristic	Number Responding	Depressed		Relative Risk	95% Confidence Bounds
		N	%		
Health and disability					
Number of medical conditions					
0	255	13	5.10	1.000	
1 or 2	1,113	144	12.94	2.772	1.545-4.975
3	391	90	23.02	5.566	3.037-10.200
4 or more	378	114	30.16	8.038	4.413-14.642
Change in weight in past year					
No change	1,562	220	14.08	1.000	
Gained 10 lb	323	45	24.46	1.935	1.409-2.657
Lost 10 lb	230	91	24.66	1.997	1.538-2.593
Reported hypertension					
No	1,208	184	15.23	1.000	
Yes	929	177	19.05	1.313	1.047-1.648
Sensory impairment					
None	1,031	115	11.15	1.000	
Hearing	330	38	11.52	1.044	0.707-1.541
Vision	433	101	23.33	2.423	1.804-3.256
Both	343	107	31.20	3.611	2.676-4.873
Requires nursing or personal care					
No	2,074	345	16.63	1.000	
Yes	49	15	30.61	2.208	1.190-4.099
Number of activities requiring assistance					
0	1,621	225	13.88	1.000	
1	280	71	25.36	2.105	1.553-2.852
2	116	29	25.00	2.065	1.326-3.217
3 or more	112	35	31.25	2.816	1.844-4.302
Number of problems with activities of daily living					
0	1,591	170	10.69	1.000	
1	209	60	28.71	3.361	2.394-4.719
2	100	28	28.00	3.246	2.040-5.166
3 or more	236	102	43.78	6.354	4.694-8.600
Health perceptions and practices					
Perceived control over health					
Much	510	41	8.04	1.000	
Some	994	126	13.35	1.762	1.217-2.551
Little or none	575	176	30.61	5.071	3.520-7.307
Self-perceived health					
Excellent or good	1,274	102	8.01	1.000	
Fair	614	128	20.85	3.039	2.295-4.024
Poor	237	128	54.01	13.493	9.741-18.691
Number of visits to physician in last 3 months					
0	1,043	142	12.42	1.000	
1	482	76	15.77	1.326	0.981-1.793
2	242	57	23.56	2.172	1.538-3.067
3 or more	269	85	31.60	3.256	2.385-4.446
Nights of sleep disturbance in past 2 weeks					
Difficulty falling asleep					
0	1,172	104	8.87	1.000	
2 or more	693	222	32.03	4.831	3.737-6.246
Difficulty staying asleep					
0	1,256	118	9.39	1.000	
2 or more	677	211	31.17	4.359	3.396-5.596
Waking too early					
0	1,383	144	10.41	1.000	
2 or more	506	175	34.58	4.592	3.531-5.841
Cognitive performance					
Mini-Mental State score ≤ 18					
Age=65-74 years	130	22	16.92	1.000	
Age=75-84 years	223	55	24.66	1.607	0.927-2.787
Age ≥ 85 years	104	24	23.08	1.473	0.771-2.812
Receives help managing finances					
No	1,995	309	15.54	1.000	
Yes	131	50	38.17	3.351	2.309-4.865
Forgets to take medication or pay bills					
No	1,986	300	15.11	1.000	
Yes	134	56	41.79	4.030	2.788-5.803

characteristics that might be modifiable and of other demographic characteristics, such as age and gender. The CES-D scores were regressed on the seven groups of predictor variables to compare the proportion of variance (R^2) explained by each group. The analysis indicated that the largest amount of variance was explained by health perceptions and practices ($R^2=0.229$, $F=126.70$, $df=5$, 2131 , $p=0.0001$), followed by sleep disturbance ($R^2=0.212$, $F=191.77$, $df=3$, 2133 , $p=0.0001$) and then health and disability ($R^2=0.187$, $F=54.33$, $df=9$, 2127 , $p=0.0001$). Considerably smaller contributions were made by demographic status ($R^2=0.074$, $F=24.35$, $df=7$, 2129 , $p=0.0001$), cognitive performance ($R^2=0.064$, $F=49.16$, $df=3$, 2133 , $p<0.0001$), opportunities for companionship ($R^2=0.063$, $F=15.90$, $df=9$, 2127 , $p=0.0001$), and family illness and bereavement ($R^2=0.029$, $F=21.03$, $df=3$, 2133 , $p=0.0001$).

To examine the possible interaction of these groups with each other and with the interviewers' observations, we performed stepwise regression. The groups were successively regressed in combinations of two, then three, then four, to a maximum of eight. The best four-group model—that is, the four groups that, when combined, accounted for the largest amount of variance—were interviewer observations, sleep disturbance, health perceptions and practices, and health and disability. This model explained almost 50% of the variance in depression ($R^2=0.497$, $F=6.92$, $df=21$, 2127 , $p=0.001$). Adding opportunities for companionship, cognitive performance, and family illness and bereavement accounted for only 2.9% more of the variance in CES-D scores, which was a statistically significant increase but comparatively small ($R^2=0.529$, $F=13.25$, $df=39$, 2127 , $p=0.001$). The addition of the final group, demographic status, added less than 1% ($R^2=0.533$, $F=2.10$, $df=43$, 2093 , $p=0.05$).

DISCUSSION

Our findings are consistent with the results of studies using the CES-D to examine the prevalence and predictors of depression in community elders. Aneshensel and Yokopenic (8) described a sociomedical causal model of depression in which the largest single causal effect came from physical illness. Similarly, O'Hara et al. (9) found that better health and stronger social support were associated with a lower prevalence.

Prospective studies also show significant modulation of depression by these characteristics. Lin and Ensel (11) found that changes in social support and undesirable life events influenced the remission, persistence, or worsening of depressive symptoms in the predicted direction, while Phifer and Murrell (12) found that the onset of depression was related to the additive effects of physical health, social support, and loss events. Interactive effects were found for social support and health and for social support and loss events.

This consistent interaction of physical health and

depressive symptoms has raised questions about the validity of the CES-D. In Berkman et al.'s analysis of the relationship of CES-D items to measures of illness and disability (10), virtually every item, not just the somatic items, related to illness and disability. Berkman et al. argued that, rather than invalidating the CES-D as a measure of depressive symptoms, the associations between physical and mental health in the elderly are epidemiologically and clinically important.

To clarify the relationship between physical health and depression, Kinzie et al. (13) studied 50 community residents who met the CES-D criteria for "possible depression" and the Research Diagnostic Criteria (22) for major, minor, or intermittent depression as determined with the Schedule for Affective Disorders and Schizophrenia. Fifty-two percent of the subjects were classified as having a depressive disorder associated with a medical illness or medication. In only four subjects could the diagnosis of depression be ascribed to a psychological reaction without contribution from medication or illness. In line with Berkman et al., they also suggested that the severity, course, and sequelae of "medically associated depression" may be significantly different from those in other forms of depressive illness.

The interaction between physical illness and self-reported symptoms of depression also has implications for the study of late-life mortality. Among the New Haven Established Population for the Epidemiologic Study of the Elderly, the mortality rate of the subjects who had depressive symptoms identified with the CES-D was twice as high as that of the other subjects (personal communication, A.M. Ostfeld, Aug. 24, 1987). Shekelle et al. (23) found that self-reported depressive symptoms predicted mortality and remained predictive even after age, occupational status, family history, and use of alcohol and tobacco were controlled in the analysis. More specifically, at 20 years the rate of deaths from cancer was 2.6 times as high among subjects with depressive symptoms as among other subjects (Ostfeld, personal communication). Similar findings have also been reported by Kaprio et al. (24) and Murphy et al. (25).

Beyond the scientific challenge of more accurately characterizing the phenomenology of late-life depression lie the issues of health care policy, distribution of services, and prevention of excess mortality and morbidity. Health policy based on the prevalence of major depressive disorders will be ineffective if the loss of social, emotional, physiological, and cognitive function is associated with depressive symptoms that are substantial and widespread but not congruent with a diagnosis of a current major disorder. Our data, like those of others (8, 11, 12), indicate a sizable prevalence of depressive symptoms among older adults. These symptoms are associated with an array of biological, psychological, and social characteristics but cluster around one potential area of intervention, physical health and disability. The hierarchy we describe indicates a straightforward profile of older

adults who express substantial levels of depressive symptoms—those who are sick, disabled, isolated, bereaved, and impoverished. If confirmed by prospective studies, these data can be used to identify modifiable factors that contribute to the emergence, persistence, and remission of depressive symptoms and to structure interventions to extend independent survival of older adults in the community.

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Parents' Attitudes and Patients' Behavior: A Prospective Study

Deborah A. Greenman, M.D., John G. Gunderson, M.D., and Diane Canning, A.C.S.W.

The authors studied the behavior of 67 psychiatric inpatients and the attitudes of their parents toward their hospitalization. They found that certain parental concerns at admission correlated with particular aspects of patient behavior and ability to engage in treatment during the first 6 weeks of hospitalization. These findings have implications for the management of inpatient treatment.

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In this paper we report on a study examining the widely held clinical belief that the course of a patient's psychiatric hospitalization can be influenced by the attitudes of involved parents. Although many studies have examined the impact on treatment outcome of relatives' attitudes toward the mentally ill patient (1-4), there have been relatively few studies of the impact of relatives' attitudes toward the treatment itself. Investigators have demonstrated that relatives' wishes to have a patient home predict the timing of discharge (5), that positive parental attitudes toward the hospital correlate with patient improvement (6), and that family resistance to treatment correlates with discharge against medical advice (7, 8).

In our clinical experience as inpatient administrators, negative parental attitudes toward a son's or daughter's psychiatric hospitalization and disagreement between parents about the need for hospitalization seem to lead to impulsive behaviors and greater patient resistance to treatment. Some of the key constituents of such negative attitudes seem to be 1) denial that the patient has a problem for which he or she needs treatment, 2) apprehension about the patient's anger at being hospitalized, which results in difficulty with being firm about the need for treatment (i.e., set-

ting limits), and 3) difficulty tolerating separation from the patient.

To our knowledge, with the exception of one study that examined the effect of parents' attitudes toward separation on the residential treatment of latency-aged boys (9), no study has examined the impact of parents' concerns about anger and separation or the importance of a disagreement between the parents about the need for hospitalization. Previous studies have often relied on indirect assessments of parental attitudes (ratings of other family members and social workers' ratings, for example) and have focused on correlations between parents' attitudes and subsequent treatment outcome rather than on correlations between parents' attitudes and patients' behavior. The aim of this study was to use direct assessment of parental attitudes to test prospectively the hypothesis that patients' resistance to treatment and impulsivity during the first 6 weeks of a psychiatric hospitalization would correlate with the parent attitudes of interest.

METHOD

The patients and their parents were recruited from consecutive admissions to a locked psychiatric unit at McLean Hospital. Sixty-seven (86%) of 78 admissions met the study criteria (age of 16-35 years and parents available for interview); these 67 patients were included in the study. (The nature of the study was explained to the patients and their parents, and they gave their informed consent to participation in the study.) For 13 (19%) of the patients, only one parent could be interviewed because of death (N=6), prolonged absence from the home (N=4), or refusal to participate (N=3). For the remaining 54 patients (81%), both parents participated.

The patient sample was mainly composed of young (mean age=22; range=16-32), single (N=62, or 93%), and upper-middle-class individuals admitted on a voluntary basis (N=58, or 87%) who had been hospitalized before (N=53, or 79%), who lived at home (N=52, or 78%), and who came from intact families (N=43, or 64%). The parents of 17 (25%) of the patients were separated or divorced. Most of the patients were either students (N=26, or 39%) or unemployed (N=25, or 37%) at the time of admission.

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TABLE 1. Parents' Attitudes Toward the Psychiatric Hospitalization of Their Children (N=67)

Attitude	Mothers (N=63)		Fathers (N=58)	
	N	%	N	%
Negative or unsure about need for hospitalization	11	17	11	19
Negative or unsure that the patient has a mental or emotional problem requiring treatment ^a	7	11	4	7
Concerned that the patient would be angry at parent because of hospitalization	18	29	17	29
Concerned about separation from the patient due to hospitalization	9	14	13	22

^aThis question was asked in a positive way, i.e., "Are you concerned that your son or daughter has a mental or emotional problem?" The negative responses are listed here because the negative response was of interest.

DSM-III clinical diagnoses given at discharge by the psychiatrist in charge of the unit indicated that these patients displayed a broad range of psychopathology. Thirty (45%) had some form of affective disorder: 18 (27%) had bipolar disorder, four (6%) had major depression, and 12 (18%) had dysthymic disorder. (Some patients were given more than one axis I diagnosis.) Thirteen (19%) of the patients were diagnosed as having schizophrenia, and 14 (21%) had a substance abuse disorder. Other axis I disorders were conduct disorder, generalized anxiety disorder, and adjustment disorder. About half of the patients were also given an axis II diagnosis, most often borderline personality disorder (N=16, or 24%).

At the time of admission each available parent was interviewed individually about attitudes toward the hospitalization (see table 1). In all but two instances the biological parents were interviewed; the stepfathers of two patients were interviewed because the patients had lived with them for most of their lives. Each parent was asked whether he or she had a particular concern (about anger, separation, or the presence of a mental or emotional illness requiring treatment) and, if so, to what degree that concern influenced his or her thinking about the need for hospitalization. Responses were scored on a scale from 0 (no concern at all) to 4 (a concern that markedly influenced the parent's opinion about the need for hospitalization). At the end of the interview, parents were asked for their overall opinions about the need for hospitalization. These responses were also scored on a 4-point scale on which 0=unnecessary, 2=unsure, and 4=necessary.

Patient data consisted of nine types of problem behaviors: four classified as resistance to treatment and five classified as impulsive (see table 2). The data were obtained from the patients' hospital records after the 6-week study period had ended (except for information about refused psychotherapy sessions, which was provided by the individual therapists). Some patients were unable to sign 3-day notices (statements of intent

TABLE 2. Problem Behaviors of 67 Psychiatric Inpatients

Behavior	Number of Times Behavior Occurred	Patients (N=67)	
		N	%
Resistance to treatment			
Refusal of medication	44	22	33
Refusal of psychotherapy	12	7	10
Statement of intent to leave the hospital in 3 days (3-day notice)	37	24	36
Discharge against medical advice	6	6	9
Impulsive actions			
Running away from the hospital	12	10	15
Assaultiveness	20	12	18
Self-destructiveness	31	11	16
Destruction of property	10	7	10
Use or possession of drugs and/or alcohol	13	11	16

to leave the hospital in 3 days) or refuse medication because their legal status mandated hospitalization or medication or both. Data were weighted so that an absence of 3-day notices for patients committed to the hospital (N=9, or 13%) and an absence of medication refusals for patients required to take medication or hospitalization and medication (N=2, or 3%) was less significant than for other patients in the study. Because some patients were in the hospital for less than 6 weeks, the weekly mean number of treatment-resistant or impulsive behaviors was used in the analysis rather than the total number for the 6-week study period.

Pearson correlations (two-tailed) were used to examine possible interrelationships among the parent variables and among the patient variables. Although we expected a negative attitude about the presence of an illness requiring treatment to be a constituent of negative parent attitudes toward the hospitalization, we found the correlation between them to be so high ($r=0.66$, $df=61$, $p<0.001$ for mothers and $r=0.65$, $df=55$, $p<0.001$ for fathers) that we combined these two variables for each parent into single variables representing the overall attitude of each parent toward the need for treatment. The disagreement variable was computed by taking the absolute value of the difference between the mothers' and fathers' scores on this combined variable. Because of a similarly high correlation ($r=0.53$, $df=65$, $p<0.001$) between destruction of property and drug use or possession, we combined these two variables into a single variable for antisocial actions. The parents' attitude variables were then correlated (Pearson two-tailed) with the mean scores for resistance and impulsive behaviors per week. Finally, because of the number of variables being tested, a stepwise multiple regression analysis was used to look for redundancy in the results (correlations between parent and patient variables that falsely appeared to be significant because of other correlations that existed among the variables).

TABLE 3. Results of Stepwise Regression Analysis of Correlations Between Parent and Patient Variables

Correlated Variables	Attitude of Mothers or Fathers												
	Negative or Unsure About Need for Hospitalization			Concerned That Patient Would Be Angry			Concerned About Separation			Overall			
	r ²	F	df	r ²	F	df	r ²	F	df	R	R ²	F	df
Mothers' attitude and patients' behavior													
Running away from the hospital				0.13	9.16 ^a	1, 61				0.36	0.13	9.16 ^a	1, 61
Self-destructiveness				0.05	4.13 ^b	1, 60	0.23	18.07 ^c	1, 60	0.53	0.28	11.56 ^c	2, 60
Assaultiveness	0.12	8.51 ^a	1, 60				0.03	2.08	1, 60	0.39	0.15	5.37 ^d	2, 60
Fathers' attitude and patients' behavior													
Refusal of medication	0.04	2.13	1, 54	0.06	3.55 ^c	1, 54				0.31	0.10	2.88 ^c	2, 54
Refusal of psychotherapy				0.15	7.46 ^b	1, 41				0.39	0.15	7.46 ^b	1, 41
3-Day notice	0.03	1.92	1, 53	0.17	11.06 ^a	1, 53	0.03	1.88	1, 53	0.47	0.22	5.09 ^a	3, 53

^ap<0.005.^bp<0.05.^cp<0.001.^dp<0.01.^ep<0.10.

RESULTS

The fathers' concerns about anger and separation correlated with the inpatient sons' or daughters' resistance to treatment, and the mothers' concerns about anger and separation correlated with impulsive behavior. The fathers' concerns about the patients' anger at them for the hospitalization correlated significantly with both the filing of 3-day notices ($r=0.41$, $df=55$, $p<0.005$) and refusal of psychotherapy sessions ($r=0.39$, $df=41$, $p<0.01$). There was a trend toward correlation with refusal of psychiatric medication ($r=0.25$, $df=55$, $p=0.065$) as well. The fathers' concerns about separation from the patients as a result of the hospitalization correlated significantly with the filing of 3-day notices ($r=0.38$, $df=55$, $p<0.005$). There was a trend toward correlation with refusal of psychotherapy sessions ($r=0.27$, $df=41$, $p=0.082$). The mothers' concerns about patients' anger correlated significantly with the patients' leaving the hospital impulsively ($r=0.36$, $df=61$, $p<0.005$), and the mothers' concerns about separation correlated significantly with self-destructive behavior ($r=0.48$, $df=61$, $p<0.0001$).

There were few correlations between patients' behavior and parents' attitudes about the need for treatment. The mothers' negative attitudes about the need for treatment correlated with antisocial actions ($r=0.35$, $df=61$, $p<0.005$). Parental disagreement about the need for treatment also correlated significantly with antisocial actions ($r=0.35$, $df=52$, $p=0.01$); this was the only type of impulsive behavior that correlated with parental disagreement. A Bonferroni correction for the presence of 56 possible correlations indicated that $p<0.001$ would be an appropriate confidence level. Given the pilot, exploratory nature of this study, a slightly higher p value of $p<0.005$ still seems appropriately significant.

A multiple regression analysis (see table 3) con-

firmed what the initial results suggested. Mothers' attitudes were not related to any of the patient resistance variables, whether those attitudes were considered singly (simple zero order correlations) or jointly (multiple correlations or regression). Mothers' concerns about anger and separation were related to impulsive behaviors even when statistical adjustments were made for other mother attitude variables. Similarly, fathers' attitudes were not related to any patient impulsive actions, whether those attitudes were considered singly or jointly. Although the analysis confirmed the importance of the relation between fathers' concerns about anger and both submission of 3-day notices and refusal of psychotherapy, the relationship between separation concerns and resistant behaviors was found to be a product of the high correlation between fathers' concerns about anger and separation ($r=0.68$, $df=56$, $p<0.001$).

Because of the strong correlations found for concerns about anger and separation, we reviewed the hospital record reports of the staff social workers who dealt with the parents concerned about anger and/or separation. The eight fathers who were concerned about both anger and separation were without exception overinvolved with the patients (for example, one of them slept with his son when the patient was home on pass). These fathers expressed fears to the social workers of losing their relationship with the patient as a result of the hospitalization. Both the mothers and the fathers who were concerned about anger either acknowledged or were described as having difficulty setting limits on the patient's behavior before and during the hospitalization. Four of the nine mothers who were concerned about separation rated the concern as extremely important in influencing their opinion about the need for hospitalization. All four were the mothers of patients who were self-destructive. These mothers seemed to identify with both the patient and the pa-

tient's illness and to experience the separation from the patient as a separation from a part of themselves.

DISCUSSION

We expected that negative parental attitudes (i.e., opposition to the hospitalization and denial of an illness requiring treatment) and what we understood to be partial determinants of those attitudes, namely, parental concerns about anger and separation, would correlate with most if not all of our indexes of patients' resistance and impulsivity. Instead, we found that specific concerns about anger and separation correlated with specific kinds of resistance to treatment and impulsive behavior and that overall negative attitudes toward the need for treatment tended not to correlate with the patient behaviors examined.

Although we anticipated that mothers' and fathers' concerns might well have different effects, we were impressed by the magnitude of the differences. Mothers' concerns correlated only with impulsive actions, and fathers' concerns only with resistance to the hospital's treatment prescriptions.

The multiple regression analysis showed that the impact of fathers' concerns about separation on resistance to treatment was a byproduct of a high correlation between fathers' concerns about anger and separation. In the light of our chart review examination of these fathers' relationships with their hospitalized children, this finding suggests that these fathers had difficulty supporting the treatment or setting limits about the need for treatment because they were afraid that taking such a position would anger the patient, leading to a loss of their relationship with the patient. In other words, the concern about separation reflected a deeper underlying concern that disagreement means loss. The patients then may have felt in a loyalty bind; they had to choose between their fathers and the hospital.

Anger and separation concerns were not linked for the mothers, and there was no correlation between these concerns of mothers and patients' resistance to treatment. The mothers' concerns about anger correlated with impulsive behaviors. It seems that mothers who were concerned about anger had difficulty setting limits on behavior but, unlike the situation with the fathers, this had to do with something other than fear of loss.

The correlation between mothers' separation concerns and patients' self-destructive behavior provides empirical support for clinical theories linking self-destructive behavior and separation issues. Although the link between the patients' fears of separation and self-destructive behavior has been noted for patients with borderline personality disorder (10, 11), the link between mothers' separation concerns and patients' self-destructive behavior has been less emphasized and certainly not empirically demonstrated. Our results are consistent with Doctors' notion that self-destructive

actions can represent a pathological attempt at separation, an attempt to confirm control over one's own body and the separateness of that body from the body of the mother (12).

Our negative results are also interesting. With one exception (the correlation between mothers' doubts about the need for treatment and antisocial actions), negative parental attitudes did not correlate significantly with the treatment-resistant and impulsive behavior variables. This means that a number of parents who were at least consciously in agreement with the need for treatment had sons or daughters who resisted treatment and acted impulsively. This is an important finding because it runs counter to clinical lore. Our current understanding of this finding is that the attitude at admission toward the need for treatment may be primarily dependent on such immediate factors as what occurred just before admission and may be a less valuable predictor of subsequent patient behavior than the more enduring concerns about the patient's anger and separation from the patient. The latter reflect the parents' long-term relationship with the son or daughter, whereas the former reflects the parents' relationship with the child at the time of admission. The more enduring concerns may or may not be reflected in the parents' overall attitude toward the hospitalization. We expect that the more enduring concerns may well play a more important role in the overall attitude as time goes on and the patient and family settle into the treatment program. We were surprised by the paucity of findings linking parental disagreement to patient behavior but are interested in studying further the possibly specific link between such disagreement and patients' antisocial behaviors.

Our study is limited by our selection of particular concerns and by the relatively small number of parents who expressed negative attitudes and patients who acted out or resisted treatment. Concerns that we did not address may have played a role, and parents might have been unwilling or unable to give valid responses regarding the concerns we did examine. Most important, because of the small numbers, we could not examine statistically the role that patients' sex and diagnosis played in our results. Such variables certainly affect the patient behaviors examined. For example, the six patients discharged against medical advice in this study, like those described elsewhere (8), tended to be substance abusers with a personality disorder who were admitted on an emergency basis. A high percentage of our patient group was diagnosed as having bipolar disorder, and recent research (13) indicates that such patients are more likely to be assaultive in the initial phases of hospitalization. We might well find a greater impact of negative parental attitudes within a particular diagnostic category. This would be a direction for further research.

Our study results confirm the importance of attending to the concerns of both parents of a psychiatric patient. They also suggest that the specific nature of the parents' concerns about the hospitalization may

have more of an impact than the overall positive or negative tone of the parents' attitude. It seems clear that parents' concerns about their hospitalized son's or daughter's anger and about separation from their children have different implications and probably different meanings for fathers and mothers. More work needs to be done to understand the meaning of these differences. At this point, we can say that directly questioning both parents at admission about such concerns may provide a warning about the obstacles ahead and help to lessen the risks of resistance to treatment and impulsive behaviors.

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Neuroleptic Augmentation With Alprazolam: Clinical Effects and Pharmacokinetic Correlates

Richard Douyon, M.D., Burt Angrist, M.D., Eric Peselow, M.D.,
Thomas Cooper, M.A., and John Rotrosen, M.D.

Alprazolam added to stable doses of neuroleptics in nine schizophrenic patients was associated with a 20%–30% mean reduction in positive and negative symptoms, although clinical response was variable and in some patients particularly brisk. The authors examined the possibilities of a pharmacokinetic effect of alprazolam on neuroleptic plasma levels and of a clinical effect of alprazolam. The modest increase in mean neuroleptic plasma levels did not correlate with clinical change, but those patients with the highest alprazolam plasma levels tended to show more robust clinical responses.

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Alprazolam has been shown to be a useful adjunct to neuroleptic therapy in schizophrenia. In an open trial with eight patients, Csernansky et al. (1) found a moderate improvement in negative symptoms. In a double-blind, placebo-controlled study involving two patients, Wolkowitz et al. (2) showed beneficial effects of alprazolam on negative and positive schizophrenic symptoms, which reversed with dose reduction or discontinuation. More recently, Wolkowitz et al. (3) studied 12 patients in whom alprazolam was added to stable fluphenazine regimens in a double-blind manner. Significant overall therapeutic effects occurred, and five of the 12 patients showed particularly brisk decrements in psychopathology. Csernansky et al. (4)

added diazepam, alprazolam, or placebo to neuroleptic regimens of 55 outpatients under double-blind conditions; the alprazolam-treated group showed initial reductions in withdrawal-retardation subfactor scores of the Brief Psychiatric Rating Scale (BPRS), but this improvement was not sustained throughout the 6-week course of treatment.

The possibility of a pharmacokinetic effect of alprazolam on neuroleptic plasma levels has not, to our knowledge, been examined. Possible relationships between alprazolam plasma levels and clinical response have been studied only by Csernansky et al. (4), who found an inverse correlation between alprazolam plasma levels and scores on the emotional withdrawal item of the BPRS. Thus, our goals were 1) to further explore the clinical effects of alprazolam when added to neuroleptics in schizophrenic patients, 2) to preliminarily evaluate any possible pharmacokinetic interactions between alprazolam and neuroleptic plasma levels, and 3) to study possible relationships between clinical effect and alprazolam plasma level.

METHOD

We studied nine schizophrenic patients (eight men and one woman) who ranged in age from 28 to 64 years (mean \pm SD, 47.3 ± 11.8 years) and met the Research Diagnostic Criteria (5) for schizophrenia as assessed by three of us (R.D., B.A., and E.P.). No subject showed any evidence of major medical or neurologic disease. All subjects had received neuroleptic treatment for their psychoses and had shown partial responses with some improvement in clinical status but persistence of such symptoms as flat affect, emotional withdrawal, vague disorganized thinking, and, in some cases, delusions and fewer but persistent auditory hallucinations. These patients were referred by ward psy-

Received March 7, 1988; revision received Aug. 9, 1988; accepted Aug. 25, 1988. From the Psychiatry Service, New York VA Medical Center, Manhattan, and the Manhattan Psychiatric Center. Address reprint requests to Dr. Douyon, New York University School of Medicine, Manhattan Psychiatric Center, Dunlap 14-A, Research Department, Ward's Island, NY 10035.

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TABLE 1. Pharmacokinetic Data and Clinical Response In Nine Patients Treated With a Combination of Alprazolam and Neuroleptic^a

Patient	Age (years)	BPRS Score				Abrams-Taylor Scale Score		Hamilton Anxiety Non-somatic Symptoms Score	
		Total		Negative Symptoms		Baseline	Change ^b	Baseline	Change ^b
		Baseline	Change ^b	Baseline	Change ^b				
1	57	60	-12	10	-1	19	-4	9	-3
2	54	59	-10	9	+1	18	-3	9	-3
3	29	38	-2	16	-2	29	0	0	0
4	30	60	-14	10	-5	17	-1	13	-9
5	40	42	-20	18	-9	26	-14	0	0
6	52	37	-15	10	-3	17	-13	17	-13
7	48	47	+1	12	-1	17	-5	6	0
8	61	54	-7	11	-1	19	-3	6	-2
9	58	43	-13	15	-5	22	-15	8	-6

^aPatients 1-4 and 6-9 were men; patient 5 was a woman.^bAbsolute change after 3 weeks.^cPatient 4 received 300 mg/month of haloperidol decanoate and 60 mg/day p.o. of haloperidol.

TABLE 2. Psychopathology, Extrapyramidal Side Effect, and Tardive Dyskinesia Scores and Neuroleptic Levels in Schizophrenic Patients Before and After Alprazolam Treatment

Item	N	Baseline		Week 3		Mean Change (%)	Paired t	df	p (two-tailed)
		Mean	SD	Mean	SD				
Scale									
BPRS									
Total	9	49	10	39	12	-20	4.49	8	0.002
Positive symptoms ^a	9	28	10	23	9	-20	4.05	8	0.004
Negative symptoms ^b	9	12	3	9	3	-25	2.63	8	0.03
Abrams-Taylor	9	20	4	14	7	-30	3.29	8	0.01
Simpson-Angus extrapyramidal side effects	9	1.7	2	1.6	2	-6	0.13	8	0.90
Dyskinetic movements	9	8.7	17	8.2	15	-6	0.42	8	0.69
AIMS	9	4.4	7	4.3	7	-2	0.29	8	0.80
Hamilton anxiety total	9	9.8	7.5	5.2	0.4	-46	2.02	8	0.08
Nonsomatic symptoms	9	7.5	5.5	3.5	2.4	-53	2.65	8	0.03
Somatic symptoms	9	2.3	2.5	1.6	1.9	-30	0.71	8	0.50
Neuroleptic level ^c									
Haloperidol	4	52	43	64	51	23	-3.08	3	0.54
Fluphenazine	3	4.9	4.5	6.0	3.5	23	0.28	2	0.80

^aSum of items 4, 8, 10, 11, 12, 14, and 15.^bSum of items 3, 13, 16, and 18.^cPlasma levels were not available for two patients, one who received thiothixene and one who received thioridazine.

chiatrists and psychiatric residents who were told that we wanted to study partially responsive patients with residual symptoms. All patients entered the study after they met the inclusion criteria for this project, and there were no dropouts. After neuroleptic dose and clinical status of the patient were stable for at least 4 weeks, alprazolam was added at an initial dose of 0.75 mg/day, which was raised to 2-3 mg/day as tolerated.

At baseline and weekly for 3 weeks, patients were rated with the BPRS (6), the Abrams-Taylor Rating Scale for Emotional Blunting (7), the Simpson-Angus Scale for Extrapyramidal Side Effects (8), the Dyskinetic Movements Scale (9), the Abnormal Involuntary Movement Scale (AIMS) (10), and the Hamilton Rating Scale for Anxiety (11). The raters were blind to plasma level data, but not to the fact that patients were receiving alprazolam.

Blood was drawn at baseline and at the time of the final rating to determine neuroleptic plasma levels and

at the time of the final rating to determine the plasma level of alprazolam. Haloperidol levels were determined by gas-liquid chromatography (GLC) fitted with a nitrogen phosphorus detector operated in the nitrogen mode by using a minor modification of the method of Bianchetti and Morselli (12). Fluphenazine was quantified with a radioimmunoassay procedure developed in our laboratory (13). Alprazolam was quantified by using the GLC electron capture method of Greenblatt et al. (14).

Fisher's exact tests were performed contrasting response (or no response) to alprazolam plasma levels (high or low). Alprazolam levels above the median value of 23 ng/ml were considered to be high. "Response" was defined as a decrease of 30% or more in total BPRS score, BPRS negative symptoms score, BPRS positive symptoms subscale score, the Abrams-Taylor scale score, and Hamilton anxiety scale score. We used paired t tests to study change from baseline

TABLE 1. (continued)

Dose (mg/day)		Plasma Level (ng/day)		
Alprazolam	Neuroleptic	Alprazolam	Neuroleptic	
			Baseline	Week 3
2	Fluphenazine, 120	51	11.3	9.5
3	Thiothixene, 80	23	—	—
2	Thioridazine, 400	12	—	—
2	Haloperidol ^c	16	134	150
2.25	Haloperidol, 20	77	11.6	16.7
3	Fluphenazine, 25	58	1.8	1.9
3	Haloperidol, 100	17	17.9	39
3	Haloperidol, 120	4	43.8	50
3	Fluphenazine, 30	61	1.5	2.5

(pretreatment) to week 3 (posttreatment) values. The Fisher's exact test was also used to compare response (or no response) to change in neuroleptic plasma levels. The median change of 14% in neuroleptic plasma concentration was used as a limit to separate increased and not increased levels.

This study was approved by the Subcommittee for Human Subjects at the New York Veterans Administration Medical Center. Informed consent was obtained after the procedures had been fully explained to the patients.

RESULTS

Individual psychopathology scores and doses and plasma levels of neuroleptics and alprazolam for our nine schizophrenic patients are shown in table 1. As shown in table 2, paired *t* tests revealed significant mean differences from baseline after combined alprazolam-neuroleptic treatment with respect to the patients' mean \pm SD scores on the total BPRS, on both the negative and the positive symptoms subscales of the BPRS, on the total Abrams-Taylor scale, and on the nonsomatic symptoms subscale of the Hamilton anxiety scale. The data in table 2 also show that the drug combination had no effect on the patients' mean \pm SD scores on the total Hamilton anxiety scale, on the somatic symptoms subscale of the Hamilton scale, the AIMS scale, the Simpson-Angus Scale, and the Dyskinetic Movements Scale. The mean change after alprazolam in haloperidol and fluphenazine plasma levels was 23% for both neuroleptics. In three (patients 5, 7, and 9) of the seven patients who received haloperidol or fluphenazine, neuroleptic plasma levels increased above the median change of 14%. The Fisher's exact test did not indicate significant differences between patients with increased and those with not increased neuroleptic plasma levels with respect to clinical response as indicated by their total BPRS scores ($p=0.6$), their BPRS negative symptoms subscale scores ($p=0.6$), their BPRS positive symptoms subscale scores ($p=0.6$),

their Abrams-Taylor scale scores ($p=0.6$), and their Hamilton anxiety nonsomatic symptoms subscale scores ($p=0.1$). Moreover, there were no significant correlations between change in neuroleptic plasma level and absolute or percent change in scores on 1) the total BPRS, 2) the BPRS negative symptoms subscale, 3) the Abrams-Taylor scale, and 4) the Hamilton anxiety nonsomatic symptoms subscale. Plasma levels were not available for the two patients who received thiothixene and thioridazine.

The Fisher's exact test indicated significant differences between patients with high and those with low alprazolam plasma levels on four measures of change in schizophrenic pathology: the total BPRS ($p=0.04$), the BPRS negative symptoms subscale ($p=0.04$), the BPRS positive symptoms subscale ($p=0.04$), and the Abrams-Taylor scale ($p=0.04$). Those who achieved high levels (higher than the median of 23 ng/ml) tended to be responders. For all of these measures, of the four patients with alprazolam plasma levels higher than 23 ng/ml, three were responders (patients 5, 6, and 9) and one (patient 1) was not; of the five patients with alprazolam plasma levels equal to or lower than 23 ng/ml (patients 2–4, 7, and 8), all were nonresponders. Moreover, there were significant correlations between alprazolam plasma concentrations and percent change in scores on the total BPRS ($r=0.76$, $df=7$, $p=0.02$), the BPRS negative symptoms subscale ($r=0.65$, $df=7$, $p=0.06$), and the Abrams-Taylor scale ($r=0.87$, $df=7$, $p=0.002$). Correlations between alprazolam plasma levels and percent change in scores on the BPRS positive symptoms subscale and the total Hamilton anxiety scale were not significant ($r=0.46$, $df=7$, $p=0.22$, and $r=0.22$, $df=7$, $p=0.56$, respectively).

DISCUSSION

For the group as a whole, alprazolam added to current neuroleptic therapy was associated with a 20%–30% reduction in schizophrenic psychopathology. Although this effect is generally consistent with the reports of Csernansky et al. (1) and Wolkowitz et al. (2), clinical improvement was quite variable among individual patients. In patients 5, 6, and 9 the combination of alprazolam and neuroleptic had rather dramatic effects; these three patients' scores decreased by 48%, 40%, and 30%, respectively, for the total BPRS, by 50%, 30%, and 33% for the negative symptoms subscale of the BPRS, and by 54%, 76%, and 68% for the Abrams-Taylor scale. This heterogeneity of response is strikingly consistent with recent findings of Wolkowitz et al. (4) and with the observation of Pickar et al. (15) that alprazolam-neuroleptic therapy appears to result in responsive and nonresponsive subgroups.

An effect of alprazolam on neuroleptic plasma levels may be suggested by the data. After alprazolam was added, haloperidol and fluphenazine plasma levels increased to a mean of 23% above baseline levels. Clearly,

this finding must be considered inconclusive, as it is based on results from a small number of patients.

While one might dismiss the clinical improvement seen in our sample as simply the result of increased neuroleptic levels, we think this is probably not the case. First, clinical improvement was not associated with changes in plasma neuroleptic levels. Second, the timing and the quality of the response were different from that seen with neuroleptic therapy alone. After the addition of alprazolam, responsive patients rapidly became more relaxed, spontaneous, and less guarded, had brightening and decreased constriction of affect, and showed increased socialization and affability.

The most interesting finding was the relationship between clinical improvement and alprazolam plasma levels. This relationship is consistent with the observation by Csernansky et al. (4) of an inverse correlation between scores for emotional withdrawal and alprazolam plasma level and is all the more striking because of the narrow dose range (2–3 mg) of alprazolam that we used. Clearly, this observation is preliminary and requires additional confirmation. If confirmed, however, the possibility of monitoring of alprazolam plasma levels and adjusting the dose to reach levels in the range of 60–80 ng/ml might prove to be a strategy that would increase the response rate to alprazolam augmentation therapy. Whether patients' responses to such high, titrated plasma levels would be sustained or transient, as Csernansky et al. (4) found, is difficult to predict. Possible withdrawal reactions are also a matter of concern if this approach is used.

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Social Phobic Symptoms in Patients With Panic Disorder: Practical and Theoretical Implications

Murray B. Stein, M.D., F.R.C.P.(C), Cheryl A. Shea, M.A., and Thomas W. Uhde, M.D.

Of 35 patients with DSM-III-R diagnoses of panic disorder, 16 also received diagnoses of social phobia, and 15 of these 16 reported past episodes of major depression. Only nine of the 19 panic patients without social phobia had histories of depression. The panic patients with histories of depression had significantly higher self-ratings of social anxiety and avoidance, but not agoraphobic fear and avoidance, than those without histories of depression. Panic disorder and social phobia may coexist in many cases, and the presence of social phobia may be associated with a higher morbid risk for major depression in this population.

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Panic disorder has assumed a central role in the clinical classification of anxiety disorders, according to *DSM-III-R*. Panic disorder may be associated with a number of other psychiatric syndromes, the best known of which are agoraphobia and major depression. In the last several years, needed attention has been devoted to delineating factors that contribute to the development of agoraphobia (1-3) and depression (3-5) in patients with panic disorder. In line with our ongoing interest in the longitudinal course of illness of patients with panic disorder (3, 5), we have become interested in identifying clinical factors that influence course and outcome (6-8).

Although investigators are beginning to study patients with social phobia (9, 10), little is known about the relationship of social phobia, agoraphobia, and panic disorder. For these reasons, we studied the prevalence of social phobic symptoms in patients with panic disorder. We also sought to determine the clinical significance, if any, of concurrent social phobic symptoms in these patients.

METHOD

The subjects in this study are a new cohort of panic disorder patients; none has been described in our previous reports (3). They were drawn from the pool of individuals who were evaluated for participation in the National Institute of Mental Health (NIMH) anxiety disorders program over the last 12 months. This sample consists of 35 consecutively evaluated individuals who met the *DSM-III-R* criteria for panic disorder after being interviewed with a modified version of the SADS-LA (11). All subjects were interviewed by a single investigator (M.B.S.). Subjects were excluded if they currently met the *DSM-III-R* criteria for major depression, although the patients had variable lifetime histories of depression. Our sample comprised 21 women and 14 men, and their mean \pm SD age was 37 ± 9 years (range = 20-59 years). The timing, duration, and character of prior episodes of major depression were systematically recorded with retrospective *DSM-III-R* criteria. In addition to lifetime history of major depression, the presence of concurrent psychiatric syndromes was determined, and additional diagnoses were made where appropriate. For this study, we also focused specifically on the degree of agoraphobic avoidance (classified as "none," "limited," or "extensive"). In addition, we made concurrent diagnoses of social phobia according to the *DSM-III-R* criteria.

DSM-III-R specifies that a diagnosis of social phobia can be made along with a diagnosis of panic disorder only if the patient's social fears and/or avoidance are not related to the fear of having a panic attack in such situations. In practice, we found this criterion to be highly subjective and difficult to apply. Whereas two patients were clear in their perceptions that they avoided social situations (public speaking in one case and more generalized interpersonal social contact in the other case) because they were afraid they would have panic attacks in those situations, the majority of patients could not be as explicit about their fears. For example, one patient (a 20-year-old student) began to feel embarrassed and self-conscious in the classroom and subsequently avoided class; nonetheless, he did not associate this situation with his panic attacks, which he felt occurred unpredictably. Therefore, because we were particularly interested in exploring the relationship between social phobia and panic disorder,

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we decided to suspend this *DSM-III-R* hierarchical rule for the concurrent diagnosis of social phobia.

All subjects completed several self-report measures at the time of the diagnostic interview. These included the Social Avoidance and Distress Scale (12) and the Fear of Negative Evaluation Scale (12), which both measure social-evaluative anxiety and avoidance. Also included were the Marks and Mathews Fear Questionnaire (13) and a self-report version of the Zung Anxiety Scale (14). The scores on these measures were not available to the examiner (M.B.S.) at the time of the diagnostic interview and thus did not influence the determination of clinical diagnoses.

The data analysis was designed to determine the prevalence of concurrent agoraphobia and/or social phobia in the 35 subjects with panic disorder and to examine the relationship of these and the other clinical variables to the lifetime prevalence of depression. Chi-square analysis with Yates correction or Fisher's exact test was used for categorical data. Unless otherwise indicated, two-tailed tests were used. All data are reported as mean \pm SD, and *p* values higher than 0.05 were considered nonsignificant.

RESULTS

The age at onset of panic disorder for the 35 subjects was 26.3 \pm 10.9 years (range=7–48 years), and the duration of illness was 10.8 \pm 9.3 years (range=2–42 years). Twenty-three (66%) of the 35 subjects with panic disorder met the *DSM-III-R* criteria for agoraphobia and 12 (34%) did not. The percentage of women was 74% (17 of 23) among the subjects with both panic disorder and agoraphobia and 33% (four of 12) among those with panic disorder alone (Fisher's exact test, *p*<0.05).

Sixteen (46%) of the 35 subjects met the *DSM-III-R* criteria for social phobia, and 19 (54%) did not. There were no sex differences between the subjects with and without social phobia (Fisher's exact test). There was no significant relationship between the diagnoses of agoraphobia and social phobia ($\chi^2=0.00$, *df*=1). As described earlier, because of the difficulty we experienced in determining for each case whether or not the social phobia should be considered functionally secondary to the panic disorder, we made concomitant diagnoses of social phobia in a hierarchy-free fashion. However, we were able to determine the temporal relationship between the onset of panic disorder and the onset of social phobia without having to invoke any subjective rules about which was secondary in terms of etiology or severity. In the 16 panic patients with concomitant social phobia, 11 (69%) would have met the criteria for social phobia before the onset of panic disorder. As is often the case in patients with primary diagnoses of social phobia (8, 9), the majority of these subjects described their social phobic symptoms as developing at a very early age or, even more typically, as having "always" been present.

TABLE 1. Characteristics and Anxiety Self-Report Scores of Panic Disorder Patients With and Without Histories of Major Depression

Variable	History of Major Depression				t	df
	Yes (N=24)		No (N=11)			
	Mean	SD	Mean	SD		
Age (years)						
Current	38.0	9.2	35.1	6.7	0.95	33
Onset of panic disorder	26.5	12.1	25.7	8.3	0.20	32
Duration of panic disorder (years)	11.5	10.5	9.4	6.4	0.61	32
Score on self-report measure						
Fear Questionnaire						
Global	4.7	2.0	4.7	1.7	-0.11	32
Agoraphobia	12.2	9.6	15.0	11.9	-0.72	31
Social phobia	12.9	6.5	9.2	7.2	1.47	31
Social Avoidance and Distress Scale	14.9	8.5	6.0	7.0	2.91 ^a	31
Fear of Negative Evaluation Scale	20.8	7.8	14.1	9.5	2.10 ^b	30
Zung Anxiety Scale	60.9	8.8	45.8	8.0	4.44 ^c	25

^a*p*<0.01.

^b*p*<0.05.

^c*p*<0.001.

Of the 35 subjects with panic disorder, 24 (69%) had lifetime histories of one or more major depressive episodes; 11 had never experienced episodes of major depression. Of the 24 subjects with histories of depression, 13 (54%) had experienced the first episode of major depression before or at the same time as the onset of panic disorder; the remaining 11 experienced the first depressive episode 6 months to 20 years after the onset of panic disorder.

We next examined the relationship between a history of major depression and the presence of other concurrent diagnoses in the patients with panic disorder. We found no relationship between the diagnosis of agoraphobia and a history of depression (Fisher's exact test). When the patients' agoraphobic avoidance scores were dichotomized as indicating "none or limited" or "extreme" avoidance, we still found no relationship to a history of depression ($\chi^2=0.013$, *df*=1). However, a significant relationship was observed between an additional diagnosis of social phobia and a history of depression: 15 (94%) of the 16 panic disorder patients with social phobia reported past episodes of major depression, whereas only nine (47%) of the 19 panic disorder patients without social phobia reported such histories (Fisher's exact test, *p*<0.005).

Finally, we subdivided the panic disorder patients according to affective disorder history and compared several demographic variables and self-report measures in the patients with histories of major depression with those in the patients without such histories. The results are shown in table 1. The two subgroups did not differ in current age, age at panic disorder onset, or duration of panic disorder. They also did not differ on any subscale of the Fear Questionnaire, but the pa-

tients with histories of depression scored significantly higher on several measures of social phobic symptoms (i.e., the Social Avoidance and Distress Scale and the Fear of Negative Evaluation Scale) and on a global measure of anxiety (i.e., the Zung Anxiety Scale).

DISCUSSION

Almost one-half (46%) of our 35 panic disorder patients had concomitant diagnoses of social phobia. While it is known that panic attacks can occur in patients with social phobia (10, 15, 16), little has been written about concurrent social phobia in patients with panic disorder. The authors of one study (2), examining personality disorders in patients with panic disorder, mentioned a subgroup of eight subjects (9%) with "social phobic symptoms," while another investigator (17) reported three cases in which panic disorder, social phobia, and agoraphobia overlapped. Solym et al. (10) found that 55% of a sample of patients with the presenting complaint of agoraphobia had "clinically significant social phobia," while Barlow et al. (16) were able to make additional diagnoses of social phobia in 22% of their patients with panic disorder or agoraphobia with panic. It is possible that our sample of panic patients, because they were part of an NIMH program, had an unusually high prevalence of other disorders or may in some way be an atypical sample. Our estimation of prevalence therefore requires replication in other centers. Nonetheless, our findings suggest that the coexistence of social phobia and panic disorder may be far from rare.

Our findings also shed further light on the question of which patients with panic disorder develop depression and which do not (3–8). While it might be reasonable to expect that patients with depression would have suffered from panic disorder longer than those without depression, our data did not support this expectation. The patients with and without histories of depression had had panic disorder for similar periods of time. Also, while it is conceivable that patients with more severe agoraphobic avoidance would be more likely to experience depression than patients with less severe avoidance, we found no such pattern. Thus, we find little support for the hypothesis that the depression which frequently complicates panic disorder is etiologically secondary to the long-term demoralizing effects of chronic agoraphobic avoidance.

While neither duration of panic disorder nor agoraphobic severity was related to a history of major depression, the concomitant diagnosis of social phobia was associated with a significantly greater lifetime risk for depression. The fact that the patients with histories of depression had considerably higher scores on several measures of social avoidance and anxiety than the patients without histories of depression is an independent validator of this finding. From both perspectives, the association between social phobic symptoms and a

history of major depression in patients with panic disorder is striking.

While this observed association is of considerable interest, the data should not be used, of course, to support a causal relationship. However, it is possible that in making concomitant diagnoses of social phobia, we are identifying a subgroup of panic disorder patients with a constellation of personality traits that includes low self-esteem, extreme self-consciousness, and a tendency toward negative self-appraisal (18). Such a subgroup could be at considerable risk for depression on the basis of psychological, particularly cognitive, factors. Additionally, the social isolation experienced as a result of social avoidance could contribute to a propensity for becoming depressed. Alternatively, concomitant social phobia may merely be a marker for a more severe illness. The co-occurrence of significant obsessive-compulsive symptoms has also been noted to increase the lifetime risk for depression in patients with panic disorder (7). It is possible that panic disorder complicated by the presence of any other disorder, rather than social phobia specifically, may increase the risk for depression. Nonetheless, our data, which show no relationship between concurrent agoraphobia and history of depression, suggest that this explanation is unlikely to be tenable.

It remains to be seen whether or not panic patients with concurrent social phobia respond to the same sorts of treatments used for patients with panic disorder alone; this should be systematically addressed in future studies. Further investigations should seek to clarify the relationship between panic disorder, social phobia, and major depression, making use of both biological and psychological (particularly cognitive) avenues of research.

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Childhood Sexual Histories of Women With Somatization Disorder

James Morrison, M.D.

The author interviewed 60 women with somatization disorder and 31 women with primary affective disorders who were matched for race, age at interview, and level of education to obtain their childhood sexual development histories. The two groups of women reported similar sexual experiences at similar ages, except that significantly more women with somatization disorder had been molested as children.

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Notably little attention has been paid to the childhood experiences of women who later develop somatization disorder. Of some 75 articles on somatization disorder published since the 1950s, only two (1, 2) provided data as to childhood sexual experiences. In an interview study Winokur and Leonard (1) reported that, apart from one patient who had been raped, the preadolescent sexual experiences of 14 women who met operationally defined criteria for hysteria did not differ from those reported for the general population by Kinsey in 1953. Coryell and Norton (2), in a chart-review study of patients hospitalized two generations ago, reported that 18% of the patients with somatization disorder and none of the patients with primary affective disorders had been sexually molested as children.

Childhood sexual experiences among patients with somatization disorder are of particular interest for several reasons. Most obviously, we want to learn whether patients with somatization disorder report experiences that are different from those of patients without somatization disorder. These data might also illuminate the causes of sexual dissatisfaction and unhappy marriages reported by patients with somatization disorder (1, 3). Ultimately, we want to learn whether early sexual events cause adult psychiatric disorders, among them somatization disorder. In this paper I will compare data on sexual development obtained from female patients with somatization disorder and from a

matched group of female patients with primary affective disorders.

METHOD

Women already identified by therapists as having somatization disorder were recruited from a large group psychiatric practice for a systematized study of their illness (4). All fulfilled *DSM-III* criteria for somatization disorder; other medical or psychiatric diagnoses that could better explain their symptoms and life course had been ruled out. Patients were not selected with regard to their sexual or marital histories. A total of 60 patients with somatization disorder were studied. A comparison group of 31 women with unipolar or bipolar primary affective disorders was matched with the group of patients with somatization disorder for race, age at interview, and level of education. All patients consented to participate in the study after its nature had been explained to them.

I interviewed all 91 patients; they were then given a structured interview by a female research assistant. The Renard Diagnostic Interview (5) served as the basis for this interview. It is a structured interview of more than 700 questions covering lifetime symptoms, course of illness, family history, and other material pertaining to childhood, religion, legal problems, education, and medical history. The data are collected in a format that allows diagnosis according to *DSM-III* criteria. Additional historical material augmented the sexual and marital histories of this interview schedule.

Statistical significance was determined by using Student's *t* test for parametric data and the Fisher exact probability test for nonparametric data; Bonferroni corrections were used for multiple comparisons.

RESULTS

Sexual experiences from childhood to maturity and early adult experiences with intercourse of both groups of patients are reported in table 1. Patients with primary affective disorders began most sexual activities slightly later than did patients with somatization disorder. Neither the number of patients in each group nor the age when the activity first occurred signifi-

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TABLE 1. Sexual Histories of Women With Somatization Disorder or Primary Affective Disorders

Item	Somatization Disorder (N=60)				Affective Disorders (N=31)			
	N	%	Age (years) ^a		N	%	Age (years) ^a	
			Mean	SD			Mean	SD
Played "doctor"	34	57	6.58	2.21	14	45	6.64	2.73
Exhibited self	29	48	6.28	2.03	16	52	7.06	2.67
Masturbated	34	57	13.00	6.32	19	61	14.47	8.94
Kissed	55	92	14.98	3.06	30	97	15.90	2.95
Dated	55	92	15.16	1.81	31	100	16.00	1.75
Had genital play with a male	46	77	16.50	2.93	23	74	16.82	4.43
Had intercourse without climax	52	87	17.77	3.94	27	87	18.30	2.63
Had intercourse with climax ^b	41	68	20.95	5.59	29	94	22.07	6.05
Ever molested ^c	33	55	10.38	4.18	5	16	9.33	3.51
Nonintercourse only	21	35	—	—	4	13	—	—
With intercourse	12	20	—	—	1	3	—	—
Learned facts of life	60	100	12.86	3.28	31	100	12.46	2.82
Had menarche	60	100	12.75	3.01	31	100	12.38	1.23

^aAge at first occurrence.^bSignificantly fewer women with somatization disorder reported that they experienced climax with intercourse ($p=0.045$, Fisher's exact test adjusted for multiple comparisons).^cSignificantly more women with somatization disorder reported ever having been molested ($p=0.003$, Fisher's exact test adjusted for multiple comparisons).

cantly differentiated the two groups of patients in terms of any of the usual childhood experiences with sex. The two groups experienced menarche and first learned about sex at about the same age. They also did not differ as to the sources of sex information: friends, mothers, and teachers accounted for about 70% in both groups (data not shown in the table).

A history of molestation (unwanted sexual contact with or without intercourse) was found significantly more often in the group of patients with somatization disorder (table 1). When it occurred, the average age at the time of molestation was nearly 10 years, after which sexual development continued to be about the same for the two groups up to and including first intercourse. As adults, only two-thirds of the patients with somatization disorder reported the ability to have climax with intercourse.

Molestations in the group of patients with somatization disorder were perpetrated by fathers ($N=5$, or 8%), stepfathers ($N=3$, or 5%), brothers or stepbrothers ($N=8$, or 13%), other relatives ($N=6$, or 10%), non-related juveniles ($N=4$, or 7%), or nonrelated adults ($N=17$, or 28%). (Some patients were molested by more than one perpetrator.) Molestations in the group of patients with primary affective disorders were by fathers ($N=1$, or 3%), brothers ($N=2$, or 6%), other relatives ($N=1$, or 3%), and nonrelated adults ($N=1$, or 3%).

DISCUSSION

The paucity of research into the sexual backgrounds of women with somatization disorder may stem from the traditional belief that women with hysteria have only imagined early sexual molestation. But psychiatrists traditionally believe their patients. We certainly do not lightly dismiss what is told us by a whole class of patients, a rule we should not break for patients

with somatization disorder. They relate names, dates, and specific experiences with a concreteness that is not the stuff of fantasy. Although family studies (6, 7) have linked somatization disorder to antisocial personality disorder, there is no convincing evidence that patients with somatization disorder are especially likely to lie.

The picture of the female patient with somatization disorder that emerges from the present study is not one of globally exaggerated sexual experiences. Her early voluntary sexual experiences do not differ appreciably from those of the patient with primary affective disorders. It is only with adulthood and the commencing of heterosexual intercourse that her voluntary sexual behavior may differ significantly from that of other women. Even then, the difference is principally in her expression of sexual satisfaction.

In this study the one childhood sexual experience that clearly distinguished patients with somatization disorder from patients with primary affective disorders was molestation. This probably holds true for molestation involving intercourse as well as that not involving intercourse, but the correction for multiple comparisons obscures this possibly significant difference. Because three-fourths of these experiences were perpetrated by adults, they cannot be dismissed as childish experimentation with age-mates. In all, over half ($N=33$) of the patients with somatization disorder had been sexually abused before they were 18 years old. In one out of five patients this abuse involved intercourse. Over 25% ($N=9$) reported having been molested by more than one person.

Coryell and Norten (2) reported similar findings: molestation in 18% of patients with somatization disorder but in no patients with primary affective disorders. They, too, reported that fathers had perpetrated relatively few (11%) of the incidents. Because theirs was a retrospective chart study, their figures are understandably less dramatic, but they are significant.

These authors backed away from their own findings, however, discounting them on the grounds that "questions concerning the validity of [early sexual molestation] are classic."

Although lacking data sufficient to diagnose somatization disorder, other articles nonetheless offer further evidence of the relation of childhood sexual abuse to somatization. Bryer et al. (8) found that female psychiatric inpatients who reported childhood sexual and physical abuse scored high on the SCL-90-R subscale for somatization and on the Millon Clinical Multiaxial Inventory somatoform subscale. Three papers (9–11) reported an association between hysterical seizures and sexual molestation.

Among the dissociative disorders, multiple personality disorder has been most strongly related to childhood sexual abuse. Putnam et al. (12) found that 83% of patients with multiple personality disorder had a history of sexual abuse; three-fourths of these cases involved incest. Saltman and Solomon (13) reported a history of incest in six adult patients with multiple personality disorder, and Stern (14) reported a history of incest in five of eight adult patients with this disorder. Associations with childhood sexual abuse have also been reported in a wide variety of other behaviors and psychiatric conditions, including suicidal behavior (15), prostitution (16), drug abuse and delinquency (17), chronic psychoses (schizophrenia and affective disorders) (18), posttraumatic stress disorder (19), and disorders suggestive of borderline personality disorder (20). Studies of childhood sexual abuse in nonpatient samples (21) have found depression, anxiety, and fear, not necessarily with any diagnosable adult psychiatric disorder.

The wide distribution of childhood sexual abuse makes it difficult to explain the variable outcomes reported for this type of trauma. Braun and Sachs (22) have suggested that its effects in multiple personality disorder are moderated by individual differences in the capacity to dissociate. Bliss (23) stated that most patients with multiple personality disorder could probably be diagnosed as having somatization disorder, but otherwise there is no convincing evidence that patients with somatization disorder dissociate more than average. In fact, only three of the 60 patients with somatization disorder in this current study also had multiple personality disorder (my unpublished data).

Family factors such as anger at authority figures and a family history of dissociation (22) may perpetuate multiple personality disorder. We already suspect that family factors are partly responsible for somatization disorder. These may include both genetics (6) and environmental factors such as a family tradition of illness or relatives who model illness behavior. Other factors that could differentially modify the outcome of molestation include intelligence, reported as high in multiple personality disorder (22), and sibship position, which

may be early in patients with somatization disorder (24). To explore these suggestions further will require studies of the overall childhood environment of children who subsequently develop somatization disorder.

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Positron Emission Tomography of the Cerebellum in Autism

C.W. Chris Heh, M.D., Renée Smith, B.S., Joseph Wu, M.D.,
Erin Hazlett, B.S., Andrew Russell, M.D., Robert Asarnow, Ph.D.,
Peter Tanguay, M.D., and Monte S. Buchsbaum, M.D.

On the basis of neurological evidence that autistic patients have fewer Purkinje and granule cells in the cerebellum as well as vermal cerebellar hypoplasia, the authors tested the hypothesis that autistic patients have cerebellar hypofunctioning. They used positron emission tomography of the cerebellum with ^{18}F -labeled 2-deoxyglucose to study seven autistic patients and eight age-matched control subjects. The results showed no significant difference in mean cerebellar glucose metabolism between the two groups, but all mean glucose rates of the autistic patients were either equal to or greater than those of the control subjects. The implications of these findings are discussed.

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Infantile autism is a severe developmental disorder that was first described by Kanner (1, 2). The clinical abnormalities that characterize this disorder include disturbances in motility, perception, social interactions, speech, and language (3). Although the etiology of infantile autism is unknown, it is strongly suspected that the disorder has a neurological basis (4). Post-mortem studies (5–7) have demonstrated that there are fewer than normal Purkinje and granule cells in the cerebella of autistic patients. Courchesne (8), in elaborating further, has suggested that the clinical abnormalities in autism stem from cerebellar dysfunction, whereupon there is a loss of inhibitory control due to malfunctioning of deep cerebellar nuclei. Moreover, using magnetic resonance imaging (MRI), Courchesne et al. (9, 10) found several cases of vermal cerebellar hypoplasia of lobes VI and VII in "classic" nonretarded autistic patients. Consequently, there is neuropathological and neuroanatomical evidence to suggest that cerebellar hypofunctioning (i.e., fewer Purkinje and granule cells and vermal cerebellar hypoplasia) is involved in the pathological expression of

autism. To investigate further the functional role of the cerebellum in autism, we used positron emission tomography (PET) to examine cerebellar and vermal glucose metabolism in patients with classic nonretarded autism and compared their functioning to that of age-matched control subjects.

METHOD

The autistic patients were either recruited through an advertisement in the newsletter for the National Society of Autistic Citizens or were known to our colleagues, who referred them directly to the study. The control group was also recruited through local advertisement or referred directly by colleagues. All patients were screened by telephone interview to ascertain the possible diagnosis of autism and to determine that they did not have any of the conditions that were listed in our exclusionary criteria. Patients who passed the screening then gave consent to participate in the full diagnostic protocol.

The diagnostic protocol consisted of independent videotaped interviews of the patient and his or her parent that were based on the semistructured Interview for Childhood Disorders and Schizophrenia (A.T. Russell et al., paper presented at the annual meeting of the American Academy of Child Psychiatry, Los Angeles, Oct. 15–19, 1986). The parents and the subjects were asked to comment on symptoms that were currently present as well as to recall symptoms that had occurred during the subjects' childhood. Past records were also obtained to verify the histories. The interviews and collateral material were rated and reviewed to establish childhood and current diagnoses. The two experienced clinician interviewers and one of the authors (A.R.), a child psychiatrist, reached full agreement on final diagnoses. The three diagnostic raters had previously established satisfactory interrater reliability ($\kappa=0.89$) in a larger study of autistic and schizophrenic subjects in which the identical protocol was used.

There were seven adult patients (five male and two female; mean \pm SD age = 23 ± 6 years, range = 19–36) and eight age-matched control subjects (seven male and one female; age = 24 ± 5 years, range = 20–35). The exclusionary criteria were past or current history of

Received Jan. 25, 1988; revision received Aug. 22, 1988; accepted Aug. 25, 1988. From the University of California, Irvine, Brain Imaging Center and the University of California, Los Angeles, Neuropsychiatric Institute. Address reprint requests to Dr. Heh, Department of Psychiatry, UCI Medical Center, Bldg. 2, Route 88, Orange, CA 92668.

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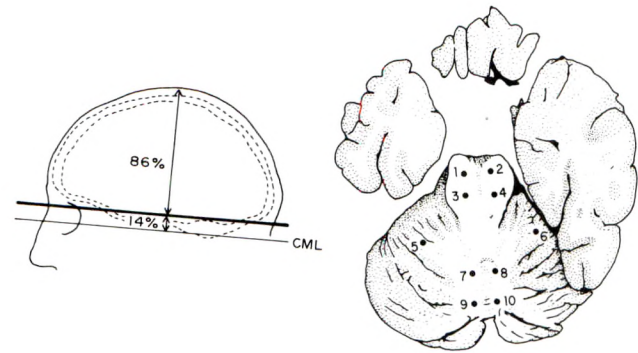
seizure disorder; known neurological, infectious, or metabolic disease; mental retardation (full-scale IQ <70); use of antipsychotic drugs or alcohol or drug abuse; and head trauma. All patients and control subjects underwent physical examinations and laboratory tests to assure that they were currently in good health. In addition, the control subjects were interviewed by a psychiatrist to assure that there was no evidence of substantial affective disorder, schizophrenic disorder, or personality disorder. On the WAIS-R the seven patients had a mean \pm SD verbal IQ of 91 ± 25 (range = 72–131) and performance IQ of 94 ± 19 (range = 75–132).

On the basis of the diagnostic protocol we have described, all seven patients retrospectively met the full *DSM-III* criteria for autism during their childhoods. As adults, at the time of interview, five of the seven continued to meet the full criteria. One subject met the criteria for autism, residual state. The seventh subject met the criteria for autism but also presented with a complex symptom picture including possible auditory hallucinations.

Each patient and control subject, all of whom had fasted at least 4 hours, had an intravenous line of 0.9% saline drip inserted into the left arm for blood sampling and another line inserted into the right arm for injection of ^{18}F -labeled 2-deoxyglucose. The subject was then seated in a darkened isolation room; the left arm was wrapped in a hot pack for arterialization of venous blood and was extended through a slit in a 6-foot-high black curtain to conceal the blood sampling activity. Two to three minutes before the injection of [^{18}F]2-deoxyglucose, the room lights were extinguished and the subject was given instructions for the Continuous Performance Test (11) and a trial run of the test. The Continuous Performance Test is a visual vigilance task that requires the subject to monitor a series of projected blurry visual stimuli (the numbers 0 through 9) on a screen. During this task the subject is instructed to push a button to signal the recognition of a predesignated target stimulus (the number 0). The target stimulus was presented irregularly, with a probability of occurrence of 0.25. After the injection and during the uptake, the investigators did not speak to the subjects, and all subjects remained quiet and cooperative while they completed the 30- to 35-minute test, as previously described in more detail by Buchsbaum et al. (12).

After uptake of the [^{18}F]2-deoxyglucose and completion of the Continuous Performance Test, the subjects were transferred to the scanning room. Nine planes parallel to the canthomeatal line were scanned by a NeuroECAT IV between 45 and 100 minutes after the injection. All slices were done with shadow shields and septum shields in a configuration with measured in-plane resolution of 7.6 mm and axial resolution of 10 mm. The slices started at 95 mm above the canthomeatal line and were done at 10-mm increments, resulting in slices at 95, 85, 75, 65, 55, 45, 35, 25, and 15 mm.

FIGURE 1. 0°12 PET Slice of the Brain^a



^aFrom the Matsui and Hirano atlas (15). Dots 1, 2, 3, and 4 are left anterior pons, right anterior pons, left posterior pons, and right posterior pons, respectively. Dots 5 and 6 are left cerebellar and right cerebellar hemispheres, respectively. Dots 7 and 8 are left and right white matter, respectively. Dots 9 and 10 are left and right vermal lobes VI and VII, respectively. CML=canthomeatal line.

Scans were transformed to glucose metabolic rates according to the model of Sokoloff et al. (13), in which we used our adaptation of a program developed by Sokoloff. Kinetic constants and lumped constants, as described by Phelps et al. (14), were also incorporated.

To survey the cerebellum and the vermis, we chose one slice in a standard brain atlas (15) to be our prototype. The slice is designated as 0°12 in the atlas and is at the level of 14% of total head height above the canthomeatal line, typically about 2 cm. It contains the following structures: cerebellum, superior posterior vermis (lobes VI and VII), superior cerebellar peduncle, pons, and chiasmatic cistern. Because of differences in both head height and brain proportion, slices for analysis were chosen on the basis of their resemblance to the prototype slice from the atlas. They were selected by a rater without knowledge of the subjects' diagnoses.

The slice from the atlas was photographed, digitized, filtered by a moving average, and stored for reference. Next, the subject's cerebellum was outlined by means of a computer algorithm, as in Buchsbaum et al. (16). The vertical meridian was fitted by least squares regression to the midpoints of line segments joining the right and left edges for each pixel row of the image. This line was bisected and a horizontal 90° meridian calculated. Then, under cursor control, a 3×3 pixel box (0.3 cm³ voxel) was placed on the regions of interest, as shown in figure 1. The proportional locations of these boxes in the anteroposterior and lateral positions were then transferred automatically to the PET slice, and mean glucose metabolic rates were calculated for the boxes on the left and right sides (the right side as a mirror image of the left around the vertical meridian). Next, the entire slice was outlined by means of a computer algorithm, as in Buchsbaum et al. (16).

We carried out analyses on both the absolute metabolic rate and the relative rate, expressed as the rate for

TABLE 1. Mean Relative Glucose Metabolic Rates^a of Seven Autistic Patients and Eight Control Subjects

Region of Interest	Relative Glucose Metabolic Rate							
	Autistic Patients				Control Subjects			
	Left Side		Right Side		Left Side		Right Side	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anterior pons	0.56	0.18	0.60	0.09	0.48	0.13	0.58	0.11
Posterior pons	0.65	0.17	0.68	0.13	0.61	0.14	0.68	0.18
Cerebellar hemisphere	0.66	0.18	0.61	0.18	0.60	0.14	0.55	0.10
White matter	0.88	0.20	0.86	0.19	0.81	0.23	0.80	0.30
Vermal lobes VI and VII	0.77	0.13	0.73	0.15	0.75	0.24	0.72	0.17

^aAt the 0°12 PET slice of the brain.

the region of interest divided by the mean glucose metabolic rate of the whole brain. The whole brain rate was approximated as the average glucose metabolism for the three PET slices at the supraventricular, mid-ventricular, and infraventricular levels. The corresponding levels from the atlas are, respectively, 61%, 41%, and 28% of the total head height above the canthomeatal line.

Glucose data were analyzed by means of repeated measures analysis of variance (ANOVA) (BMDP, program 2v [17]) and post hoc *t* tests (program P3D). We chose ANOVA because the regions of interest were arranged anteroposteriorly in right-left pairs, providing natural factors with repeated measurement. All tests of significance were two-tailed at the 0.05 level, and the Huynh-Feldt factor (17) was applied to correct for inflated degrees of freedom. The anteroposterior positioning began with the pons as the most anterior, followed by the cerebellar hemispheres and then the white matter, and, finally, the vermal lobes as the most posterior (see figure 1).

RESULTS

A three-way ANOVA, with independent groups (autistic patients versus normal control subjects) and factors of hemisphere (left, right) and anteroposterior position (pons, cerebellum, white matter, vermal lobes) was performed, with repeated measures of relative metabolism (the rate for the region of interest divided by the whole brain rate) for the previously noted brain structures at the 14° PET slice. There was no overall significant group effect ($F=0.31$, $df=1, 13$, $p=0.59$). The Anteroposterior Position by Group interaction ($F=0.18$, $df=4, 52$, $p=0.95$), the Hemisphere Position by Group interaction ($F=0.85$, $df=1, 13$, $p=0.37$), and the Anteroposterior Position by Hemisphere by Group interaction ($F=0.25$, $df=4, 52$, $p=0.91$) were all nonsignificant (see table 1). Results of an unpaired *t* test for the relative whole cerebellar metabolic rate (the whole cerebellar rate divided by the whole brain rate) of the autistic patients ($\text{mean} \pm \text{SD} = 0.72 \pm 0.11$) versus that of the control subjects (0.70 ± 0.17) was also nonsignificant ($t=-0.39$, $df=14$, $p=0.70$). Analyses of the rates relative to the whole cerebellar rate

(the rate for the region of interest divided by the whole cerebellar rate) and analyses of the absolute metabolic rates for the regions of interest also showed no significant differences between the normal control subjects and the autistic patients.

DISCUSSION

The results demonstrate that the relative glucose metabolism for these autistic patients in the area of the cerebellum and vermal lobes VI and VII was not lower than that for normal age-matched control subjects. This is not a direct refutation of Courchesne's hypothesis, since MRI confirmation of the location of the cerebellum and vermal lobes was not obtained. The evidence reported earlier (5-7) of cerebellar vermal hypoplasia and a paucity of Purkinje and granule cells in the cerebella of autistic patients would lead one to expect decreased glucose metabolism, which we did not find. In fact, although no statistically significant difference was found between the control subjects and the autistic patients, a close inspection of table 1 shows that all the mean glucose rates for the autistic patients were either equal to or greater than those for the control subjects. In a study by Rumsey et al. (4), the cerebellar glucose rate for autistic subjects was greater than for control subjects but did not reach statistical significance. Thus, in studies using PET, there has been no evidence for lower glucose metabolism in the cerebella of autistic subjects than of control subjects.

In this study, subjects performed a visual vigilance task, the Continuous Performance Test, rather than undergoing a test of cerebellar motor function such as finger to nose. This might have diminished our chances of finding a significant difference between groups, since cerebellar function might not have been enhanced or stressed. However, Courchesne et al. (10) suggested a possible relation between behavioral attention and developmental brain processes involving the cerebellum. At the very least, the Continuous Performance Test standardized each subject's psychological state and controlled motor activity, both of which are potential sources of variation.

It is interesting to compare autism to other neurodevelopmental disorders such as Down's syndrome.

Schwartz et al. (18) showed that young patients (N=4, ages 19–27 years) with Down's syndrome also had elevated metabolic rates according to PET; Rumsey et al. (4) had noted this in autistic patients. We speculate that these brain areas of elevated glucose metabolism may represent "islands" of inefficient brain metabolism, which are perhaps the sites of early neurodevelopmental insult, resulting in redundant and poorly integrative neural circuits. Schwartz et al. suggested that the elevated metabolic rates may represent increased neuronal activity in redundant circuits.

Only with MRI confirmation of the location of the cerebellum and other brain structures and with larger sample sizes will PET studies help to definitively elucidate the metabolism of various brain structures and their relation to autism. Furthermore, studies addressing the methodological difficulties of comparing anatomical structures on the midsagittal and parasagittal MRI slices would also be helpful.

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High Prevalence of Obsessive-Compulsive Symptoms in Patients With Sydenham's Chorea

Susan E. Swedo, M.D., Judith L. Rapoport, M.D., Deborah L. Cheslow, B.S.,
Henrietta L. Leonard, M.D., Elia M. Ayoub, M.D.,
Don M. Hosier, M.D., and Ellen R. Wald, M.D.

The 20-item Leyton Obsessional Inventory—Child Version was completed by children and adolescents who had had Sydenham's chorea (N=23) or rheumatic fever without chorea (N=14). The Sydenham's chorea subjects had significantly more obsessive thoughts and compulsive behaviors and significantly greater interference from these behaviors. Three Sydenham's chorea patients but no rheumatic fever patients had substantial obsessional interference and met criteria for obsessive-compulsive disorder when interviewed by telephone. This suggests that obsessive-compulsive disorder, at least in some patients, may be due to basal ganglia dysfunction.

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Sydenham's chorea is a neurological disorder characterized by sudden involuntary jerking movements of the extremities. Also known as "St. Vitus dance," it can have a gradual or acute onset and may manifest itself as subtle deterioration of handwriting, choreiform movements released by stressful examinations, or violent, continuous flailing of the arms and legs (1). This movement disorder, primarily seen in prepubertal girls, is rare in blacks and adults, although recrudescence of symptoms during adulthood, as chorea gravidarum, has been reported (2). It occurs in 10%–30% of children with rheumatic fever (3) and may serve as a sole diagnostic criterion for acute rheumatic fever.

The clinical presentation implicates dysfunction of the basal ganglia. In a landmark study, Husby et al. (4) found that antibodies directed against the cytoplasm of the subthalamic and caudate nuclei were present in the sera of nine (41%) of 22 children with chorea, seven

(14%) of 50 samples from children with carditis, and none of the samples from healthy control subjects.

Obsessive-compulsive disorder occurs in childhood and adolescence; its estimated prevalence in adolescents is 0.4% (5). It is rare in blacks. The disorder is characterized by repetitive, intrusive thoughts (obsessions) and time-consuming, senseless, complex rituals (compulsions). In children, as in adults, the most common obsessions concern contamination and harm coming to one's self or others. Rituals most often involve washing, checking, counting, or repetitive movements. The obsessions and compulsions are considered senseless and irrational by the patients but irresistible in force.

An association between obsessive-compulsive disorder and Sydenham's chorea was noted in 1958 (6), in a study of eight children with Sydenham's chorea, four of whom had significant obsessive symptoms, including washing and ordering rituals. Conversely, in a comparison of the prevalence of neurological illness in obsessional and nonobsessional psychiatric patients (7), six of 105 obsessional patients had histories of Sydenham's chorea, compared with only two of 105 psychiatric control subjects. Finally, in a follow-up study by Freeman et al. (8), the psychological states of 40 adults with childhood histories of Sydenham's chorea were compared with those of 40 control subjects who had been hospitalized for glomerulonephritis, rheumatic fever, or osteomyelitis during the same period. "Personality disorders," including compulsive personality, were seen in 26 of the 40 chorea patients but only eight of 30 control subjects, and "psycho-neurosis" (phobias, obsessive-compulsive symptoms, conversion, and anxiety) was reported in seven of the 40 chorea patients but in no control subjects.

Recent outbreaks of rheumatic fever and Sydenham's chorea at various sites (3, 9, 10) provided an opportunity to conduct what we believe to be the first systematic study of obsessive-compulsive disorder in Sydenham's chorea. The present study was a comparison of ratings on standardized scales of obsessive-compulsive symptoms in children who had had Sydenham's chorea and children who had had rheumatic fever without chorea.

Received Feb. 16, 1988; revised July 13, 1988; accepted Aug. 10, 1988. From the Child Psychiatry Branch, NIMH; the Department of Pediatrics, University of Florida College of Medicine, Gainesville; the Department of Pediatrics, College of Medicine, Ohio State University and Children's Hospital, Columbus; and the Ambulatory Care Division, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Swedo, Child Psychiatry Branch, NIMH, Bldg. 10, Rm. 6N240, 9000 Rockville Pike, Bethesda, MD 20892.

METHOD

Three sites with recent outbreaks of rheumatic fever and Sydenham's chorea collaborated in this study. All the patients with either diagnosis who could be located were included; 39 Sydenham's chorea patients and 21 patients who had had rheumatic fever without chorea. Of these, 15 with Sydenham's chorea and seven with rheumatic fever were lost to follow-up, and one Sydenham's chorea patient refused to participate, leaving 23 Sydenham's chorea patients and 14 with rheumatic fever. Letters of explanation were sent to the parents of minor children requesting them to pass the standardized questionnaires on to their children. All parents agreed to do this. The children were each paid \$10.00 upon receipt of their completed questionnaires.

In the Sydenham's chorea group, there were 13 females and 10 males, and their mean \pm SD age at onset of illness was 10.00 ± 2.9 years (range=6–15). The rheumatic fever group comprised five females and nine males, and their age at onset was 10.08 ± 2.4 years (range=7–15). The interval between onset of illness and questionnaire completion was longer for the Sydenham's chorea group (66.5 ± 69.9 months) than for the rheumatic fever group (32.6 ± 41.5 months) but not statistically significantly different.

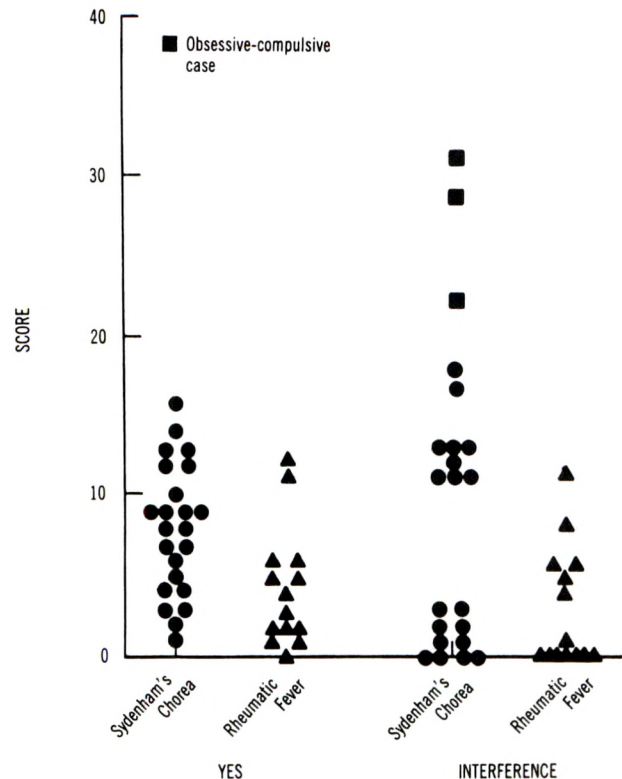
The parents of each patient were asked to complete a checklist taken from the Yale-Brown Obsessional Inventory (S. Rasmussen and W. Goodman, personal communication, 1987). They were asked to indicate which habits had noticeably interfered in their child's life during the illness or were presently a problem.

The patients completed a standardized questionnaire assessing anxiety, depression, and obsessiveness. The 20-item Leyton Obsessional Inventory—Child Version (11), for which age and sex norms were available from a recent epidemiologic study (12), provided quantifiable information about obsessiveness during the episode of chorea. The "yes" score indicates the number of obsessive thoughts or compulsive behaviors, and the "interference" score indicates the degree of interference resulting from these behaviors. Questions from a standardized modification of the Diagnostic Interview for Children and Adolescents (13) were included to elicit current and lifetime histories of anxiety, depression, conduct disorder, attention-deficit disorder, and emotional lability.

Children reporting more than 10 symptoms (yes score > 10) or having an interference score of at least 15 were interviewed by telephone with a structured diagnostic interview (5). One Sydenham's chorea patient requested a complete evaluation for obsessive-compulsive disorder and is described later in this article. A subgroup of children were selected at random from the low-scoring group and were interviewed by telephone.

Because we predicted that the Sydenham's chorea group would score higher on the obsessiveness inventory than the rheumatic fever group, a one-tailed Stu-

FIGURE 1. Scores on the Leyton Obsessional Inventory—Child Version of Children and Adolescents With Histories of Sydenham's Chorea (N=23) or Rheumatic Fever (N=14)^a



^aThe "yes" score is the number of obsessive thoughts or compulsive behaviors, and the "interference" score indicates the degree of interference resulting from these behaviors.

dent's *t* test was used for these statistical comparisons; two-tailed *t* tests were used for the other comparisons.

RESULTS

The patients with histories of Sydenham's chorea scored higher on both obsessiveness scales than did the rheumatic fever comparison group, as shown in figure 1. The difference in mean score was significant for both the yes item (mean \pm SD = 8.00 ± 4.1 and 4.29 ± 3.6 ; $t = 5.58$, $df = 35$, $p = 0.004$) and the interference item (9.64 ± 9.4 and 2.93 ± 3.7 ; $t = 6.02$, $df = 34$, $p = 0.003$).

The Sydenham's chorea patients also had significantly higher mean scores on the depression scale (mean \pm SD = 1.48 ± 1.2 and 0.50 ± 1.0 ; $t = 2.54$, $df = 35$, $p = 0.02$) and the anxiety scale (1.22 ± 1.1 and 0.50 ± 0.9 ; $t = 1.99$, $df = 35$, $p = 0.05$).

Five of the 23 Sydenham's chorea subjects and none of the 14 rheumatic fever comparison subjects had obsessional interference scores of 15 or more. According to the structured interviews, none of the low scorers had any obsessive-compulsive symptoms and the subjects with the three highest interference scores had clin-

ically diagnosable obsessive-compulsive disorder. One such high scorer was a 7-year-old boy who had become obsessed with dirt and contaminants. The interference from his washing rituals was striking; his compulsion to wash his and his brother's socks was particularly time-consuming. An adolescent girl recalled having had obsessions about her family's safety and compulsive checking rituals for several months after her chorea. The third case, that of a 12-year-old girl, is presented in more detail.

CASE REPORT

Sarah developed Sydenham's chorea at the age of 10. The chorea consisted of constant motor activity and random, involuntary flailing of her arms and legs. Haloperidol (0.5 mg b.i.d.) decreased her motor symptoms. Six months after the onset of her chorea, she was free of motor abnormality, and the medication was discontinued.

Troublesome obsessions had begun 2 weeks before the onset of the motor symptoms. Recurrent thoughts of harm coming to her parents and violent sexual images plagued her. The frequency of these obsessive thoughts lessened over the ensuing year. During the 12 months before evaluation, she had only rare obsessive thoughts, but her difficulty with concentration continued.

Ritualistic behavior remained Sarah's major problem and included ordering and repeating rituals. She compulsively ordered and reordered the books in her book bag for 2 hours or more each evening. She felt compelled to get the books "just right" but found this so annoying that she dreaded doing her homework, and her grades slipped. She also repeated her schoolwork until each paper was "perfect." The forms of numbers had to be perfect, and there could be no stray ink marks, dark spots, or smudges. Her other ordering rituals were arranging the contents of her purse and jewelry boxes and aligning her stuffed animals.

DISCUSSION

The high prevalence of obsessive-compulsive features among patients with histories of Sydenham's chorea is intriguing and supports other evidence linking obsessive-compulsive disorder and disease of the basal ganglia. Although the Sydenham's chorea patients in our study had significantly higher depression and anxiety scores than the comparison subjects, none was clinically depressed or anxious. The high depression and anxiety scores may be secondary to the neurologic process of Sydenham's chorea or, as is frequently seen in patients with obsessive-compulsive disorder, may be secondary to the obsessive-compulsive symptoms. However, the possibility that anxiety or depressive symptoms are themselves attributable to an autoimmune mechanism cannot be ruled out.

Subjects with histories of rheumatic fever are an ideal comparison group for patients with Sydenham's chorea because if some psychological trauma were responsible for the obsessive-compulsive symptoms, the

groups should be equally vulnerable. Both illnesses are secondary to streptococcal infections and autoantibody formation; the salient difference is the presence of anticaudate and antisubthalamic nuclei antibodies in Sydenham's chorea and the absence of these antibodies in rheumatic fever without chorea (4). The specificity of obsessional symptoms in Sydenham's chorea is compelling evidence for basal ganglia dysfunction in obsessive-compulsive disorder.

The autoantibody hypothesis was independently tested in a group of 12 children with obsessive-compulsive disorder. Indirect immunofluorescent examination of the serum of these patients by E. Kemeny (Rockefeller Institute, New York) failed to demonstrate the presence of anticaudate antibodies (4). This may have been due to the extended intervals between the onsets of the patients' illness and the collection of their serum samples; patients must have been sick for at least 1 year before entering the NIMH study.

Other evidence for basal ganglia involvement includes the high prevalence of obsessive-compulsive symptoms in patients with Tourette's syndrome, the presence of choreiform movements in 33% of 55 children with obsessive-compulsive disorder, and neurologic deficits, including tics and neurodevelopmental delay, in 80% of these patients (14). There have also been several case reports of obsessional illness in patients with demonstrable basal ganglia lesions after carbon monoxide poisoning or wasp stings (15). Abnormally rapid glucose metabolism in the caudate nuclei and orbital gyri shown on PET scans (16) and small caudate size shown in CT scan volumetric analyses (17) have been reported in patients with obsessive-compulsive disorder. Thus, clinical, anatomic, radiologic, and psychologic data implicate the basal ganglia in obsessive-compulsive disorder.

To address the intriguing questions raised by this study, a prospective study of acute cases of Sydenham's chorea and obsessive-compulsive disorder is underway to document the formation of autoantibodies against the basal ganglia structures in those Sydenham's chorea patients demonstrating obsessive-compulsive symptoms and to trace the natural history of the obsessional symptoms in Sydenham's chorea.

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Water Excretion and Plasma Vasopressin in Psychotic Disorders

Robin Emsley, M.B., Ch.B., M.Med.(Psych.), M.D.,
Annemarie Potgieter, M.B., Ch.B., Frans Taljaard, M.B., Ch.B., M.D.,
Gina Joubert, B.Sc., and Richard Gledhill, B.Sc., M.D., M.R.C.P.

To investigate the pathogenesis of water intoxication in psychotic disorders, a standard water load test was given to 23 unmedicated patients with schizophrenic or schizoaffective disorders. Levels of plasma arginine vasopressin were measured concurrently. Compared with 28 healthy volunteers, the psychotic patients had significantly smaller cumulative urine output and higher minimum urine osmolalities. Patients whose current illness had lasted less than 24 weeks exhibited the most severe antidiuretic state and also had the highest plasma arginine vasopressin levels. Water intoxication in acute exacerbations of psychosis may develop as a result of impaired excretory mechanisms.

(Am J Psychiatry 1989; 146:250-253)

Self-induced water intoxication is a well-recognized complication in certain patients with psychotic disorders, particularly of the schizophrenic type (1-3). Initially, polydipsia was emphasized in the pathogenesis (4), but it was later recognized that impaired excretory mechanisms may also play a role. Lack of maximal urinary diluting capacity in the presence of serum hypotonicity in some cases suggested an excessive secretion of arginine vasopressin. In fact, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has subsequently been documented by direct assay of arginine vasopressin in a number of psychotic patients with water intoxication (5, 6). In a further development, Raskind et al. (7) reported elevated plasma arginine vasopressin levels in unmedicated, acutely psychotic patients without water intoxication. This led us to investigate the existence of an antidiu-

retic state in psychotic patients by measuring their responses to a standard water load test (8) and estimating concurrent levels of plasma arginine vasopressin. Reference data were obtained by simultaneously studying a group of healthy volunteers.

METHOD

The psychotic patients consisted of 16 men and seven women between the ages of 18 and 42 years (median=27 years) who met the Research Diagnostic Criteria (9) for a schizophrenic (N=15) or schizoaffective (N=8) disorder. All of them manifested features of active psychosis, had been free of psychotropic medication for at least 4 months, and were tested within 4 days of admission to a psychiatric ward. At the time of the study, each patient was rated on the Brief Psychiatric Rating Scale (BPRS) (10). The healthy volunteers were recruited from hospital staff and their families; there were 21 men and seven women between the ages of 18 and 55 years (median=25.5 years). Subjects in both groups were in good physical health, did not display polydipsia, and had no other disorders associated with an abnormal fluid balance or with SIADH. None gave a history of excessive alcohol consumption or drug abuse or was taking any medication. All subjects gave informed consent.

The subjects fasted and abstained from smoking from the previous evening until completion of the test, during which they remained recumbent. Blood and urine samples were obtained before the administration of a standard water load test. Blood was analyzed for sodium, potassium, creatinine, urea, osmolality, glucose, albumin, globulin, conjugated and unconjugated bilirubin, γ -glutamyltransferase, hematocrit, thyroid-stimulating hormone, T_3 , T_4 , 9-hour cortisol, plasma renin activity, and β_2 microglobulin (as an indicator of glomerular function). Urine was analyzed for osmolality and β_2 microglobulin (as an indicator of renal tubular function).

For the water load test, subjects consumed 20 ml/kg of body weight of cool tap water within 15 minutes. Each hour during the next 4 hours, blood pressure was recorded and samples of blood and total urine output

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were collected. These were analyzed for electrolyte and osmolality concentrations. Blood for arginine vasopressin assay was drawn at 0, 2, and 4 hours and was collected in ice-cooled EDTA Vacutainer tubes. These were immediately transported on ice to the laboratory, and the plasma was separated in a cold centrifuge at 4 °C. The separated plasma was stored at -20 °C. Arginine vasopressin was measured by means of a radioimmunoassay kit (Immuno Nuclear Corp.). Interassay and intra-assay coefficients of variation were 12.5% and 11.2%, respectively.

To determine the relationships between the variables of anxiety, psychotic symptoms, and response to the water load test, the following procedure was followed. A total anxiety factor, consisting of the sum of the scores from the BPRS scales of anxiety, agitation, and excitement, and a psychosis factor, consisting of the sum of the scores from the BPRS scales of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization (7), were calculated. Correlations were then sought between these scores and the percentage water load excreted, the minimum urine osmolality obtained, and plasma arginine vasopressin values at 0, 2, and 4 hours.

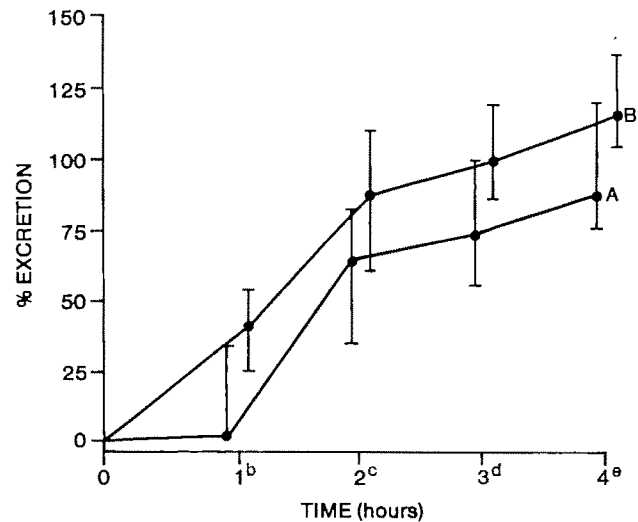
Because of small sample sizes, the median and interquartile ranges were used to summarize the continuous measurements within the groups. Pairwise comparisons were done with the Mann-Whitney U test or, when there were many tied values, the Median test (11). Spearman correlation coefficients (ρ) for selected continuous variables were calculated within each group. A significance level of 0.05 was used throughout.

RESULTS

Values for baseline blood and urine studies were within normal limits in all of the subjects. The percentage water load excreted and the minimum urine osmolalities obtained in the two groups of subjects are shown in figures 1 and 2. Compared with healthy volunteers, the psychotic patients excreted a significantly lower cumulative volume (for healthy volunteers, median=115% and interquartile range=32; for psychotic patients, median=86% and interquartile range=44). The psychotic patients also had significantly higher minimum urine osmolalities (for healthy volunteers, median=72 mmol/kg of water and interquartile range=18; for psychotic patients, median=112 mmol/kg and interquartile range=161). Figure 3 shows plasma arginine vasopressin levels measured at 0, 2, and 4 hours. Median and interquartile range values at 0, 2, and 4 hours for the psychotic patients were 1.30 and 1.80 pg/ml, 0.90 and 0.70 pg/ml, and 1.00 and 0.90 pg/ml, respectively; for the healthy volunteers, they were 1.15 and 0.58 pg/ml, 0.90 and 0.63 pg/ml, and 0.99 and 0.84 pg/ml, respectively. There were no significant differences between the two groups.

Baseline serum sodium levels for the psychotic patients (median=142 mmol/liter and interquartile range=

FIGURE 1. Percentage Water Load Excreted for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe closed circles represent group median values; the lower bars, 0.25 centiles; and the upper bars, 0.75 centiles.

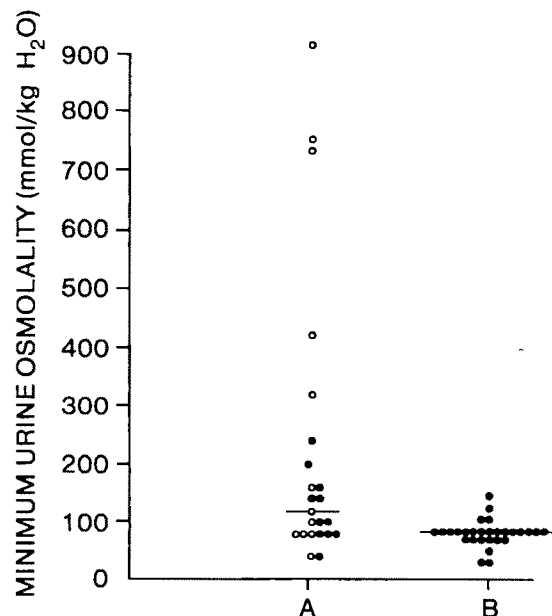
^bSignificant difference between the two groups (Mann-Whitney U=13.37, df=1, p=0.0003).

^cSignificant difference between the two groups (Mann-Whitney U=7.75, df=1, p=0.005).

^dSignificant difference between the two groups (Mann-Whitney U=9.12, df=1, p=0.003).

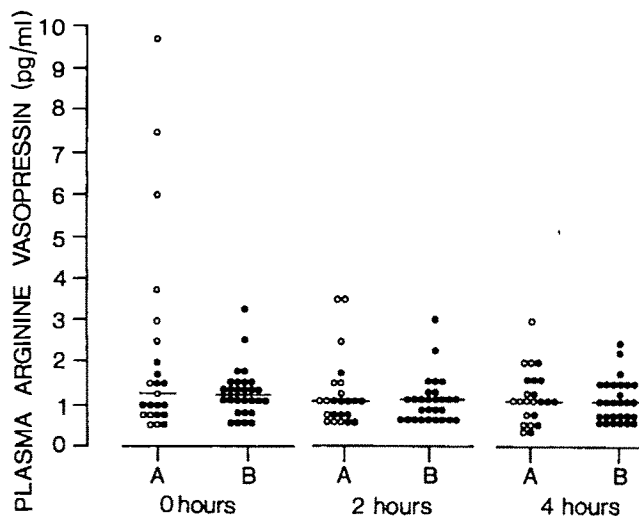
^eSignificant difference between the two groups (Mann-Whitney U=12.8, df=1, p=0.0003).

FIGURE 2. Minimum Urine Osmolalities After Water Loading for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe open circles represent individual values for patients whose current illness lasted less than 24 weeks. The horizontal bars represent group median values. Significant difference between the two groups (Mann-Whitney U=16.42, df=1, p=0.0001).

FIGURE 3. Plasma Arginine Vasopressin Levels at 0, 2, and 4 Hours During Water Loading for 23 Psychotic Patients (group A) and 28 Healthy Volunteers (group B)^a



^aThe open circles represent individual values for patients whose current illness lasted less than 24 weeks. The horizontal bars represent group median values. There were no significant differences between the two groups at 0, 2, and 4 hours.

3) were similar to those of the healthy volunteers (median=142 mmol/liter and interquartile range=5). At 4 hours, serum sodium values had reverted to baseline levels in the healthy volunteers (median=142 mmol/liter and interquartile range=5) but remained significantly lower (median test, $\chi^2=8.64$, $df=1$, $p=0.003$) in the psychotic patients (median=139 mmol/liter and interquartile range=4). The median value and interquartile range for serum osmolality before loading for the psychotic patients were 284 and 14 mmol/kg of water, and for the healthy volunteers, 285.5 and 6 mmol/kg. At 4 hours, the medians and interquartile ranges were 279 and 8 mmol/kg of water for the psychotic patients and 281.5 and 7 mmol/kg for the healthy volunteers.

The only significant correlations were between total anxiety scores and plasma arginine vasopressin at 0 hours ($\rho=0.54$, $N=23$, $p=0.007$) and at 2 hours ($\rho=0.51$, $N=23$, $p=0.01$).

On separating the psychotic patients according to duration of the current illness, those with a duration of less than 24 weeks ($N=12$) showed the most pronounced antidiuretic state. Thus, compared with the healthy volunteers, all 12 were below the 0.25 centile of 104% for cumulative urine output, 10 were above the 0.75 centile of 81.5 mmol/kg of water for minimum urine osmolality, and seven were above the 0.75 centile of 1.40 pg/ml for baseline arginine vasopressin levels.

DISCUSSION

The results of this study indicate that an antidiuretic state exists in some patients with schizophrenic and

schizoaffective disorders and that this is most pronounced in those whose current illness is of less than 24 weeks' duration. We attribute this abnormality to an arginine vasopressin mediated effect, since other, recognized causes of water excretion, such as renal, hepatic, or cardiac failure; hypothyroidism, and adrenal insufficiency (8), were not evident. Arginine vasopressin hypersecretion is suggested by the fact that the highest baseline plasma arginine vasopressin levels were found in the patients with the most pronounced antidiuretic state. However, the possibility of enhanced renal sensitivity to arginine vasopressin cannot be excluded, because levels of the hormone did not differ significantly between the psychotic patients and the healthy volunteers. In a study of water metabolism in medicated psychotic patients with polydipsia and hyponatremia (12), similar findings in conjunction with a shift in the relation between urine osmolality and plasma arginine vasopressin levels led the authors to suggest the existence in their patients of enhanced renal sensitivity to arginine vasopressin. The cause was not readily apparent. Our patients did not have polydipsia or hyponatremia and were not receiving neuroleptics. Nevertheless, enhanced renal sensitivity to arginine vasopressin remains a possible explanation for their antidiuretic state.

Seven of the 12 patients whose current illness had lasted less than 24 weeks had baseline arginine vasopressin levels above the 0.75 centile for the control subjects. Hyperosmolality, the normally overriding physiological stimulus to arginine vasopressin release, cannot be implicated because serum sodium levels were not raised. (The use in this context of serum sodium values rather than values for serum osmolality is in accordance with recommendations [8] when, as in our case, the method for determining osmolality uses serum rather than plasma and vapor pressure osmometry rather than freezing point depression.) The recognized nonosmolar stimuli of hypovolemia, hypotension, nausea, and hypoglycemia (8) were not present, while the activity of plasma renin—implicated in the control of arginine vasopressin release (13)—was not elevated. Pathways subserving osmoregulation may have been deranged. Thus, although preservation of osmoreceptor control was indicated by a fall in plasma arginine vasopressin levels at 2 and 4 hours that was appropriate to the reduced concentration of serum sodium (figure 3), the higher baseline plasma arginine vasopressin levels could be explained by a resetting of osmoreceptors, with a downward shifting of the threshold at which arginine vasopressin is released (14). In this regard, it is noteworthy that in the psychotic patients with polydipsia and hyponatremia studied by Goldman et al. (12), the osmotic threshold for arginine vasopressin release was shown to be lowered.

Nonspecific emotional stress has been proposed as a stimulus to arginine vasopressin release (15). Whereas the evidence is tenuous and may depend on the development of hypotension (16), our findings of significant correlations between total anxiety scores and plasma

arginine vasopressin levels at 0 and 2 hours suggest that emotional stress may have been relevant in this instance. Finally, some process other than the recognized osmolar and nonosmolar regulatory mechanisms may have been responsible. Raskind et al. (7) have suggested that a disturbance of CNS function may produce the symptoms of a psychotic disorder and simultaneously alter central arginine vasopressin regulation.

The finding of higher baseline plasma arginine vasopressin levels in patients with an illness of short duration accords with the fact that many reported cases of water intoxication occurred at the time of an acute psychotic episode. It could be that excessive release of arginine vasopressin is a necessary factor. Occurring during acute exacerbations and thereby rendering such individuals susceptible, the actual development of water intoxication may depend on the presence of additional factors that compromise water homeostasis. Factors that may be particularly relevant include increased fluid intake (primary polydipsia) (1), defects in urinary dilution (12), and drugs considered to be causative agents in SIADH, such as the nicotine from tobacco smoking (17), carbamazepine (18), thiazide diuretics (19), and, possibly, neuroleptic drugs (20).

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Continuing in Treatment as a Form of Selection Bias

Matthew J. Edlund, M.D., M.O.H., and Alan C. Swann, M.D.

Panic patients who continued treatment (N=12) did not have symptom scores significantly different from those of patients who declined or discontinued treatment (N=12) but they did have lower pretreatment MHPG levels. Continuing in treatment may itself cause selection bias for biochemical variables under study.

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In clinical studies, bias is produced by any factor that may make the results taken from a sampled population inappropriate or inaccurate in describing the general population of interest. One of the more common forms of selection bias is called volunteer bias, since people who volunteer for studies are often different from those who refuse. For example, in population surveys of physical health, disproportionate numbers of nonsmokers compared with smokers tend to participate, causing a bias in the reported results (1). Volunteer bias is a potential confounder in most medical treatment studies and can easily result from such issues as informed consent (2).

Most investigations of volunteer bias have looked only at subjects entering or not entering studies. To our knowledge, continuing in treatment has not been studied as a possible type of volunteer bias. We report here a study in which continuing in treatment produced volunteer bias, not for clinical symptoms, as expected, but for a biochemical variable that was a main object of study.

METHOD

Twenty-eight patients agreed to enter a study of the biology of panic disorder. Each patient signed an informed consent statement and received a free consultation visit with no obligation for future visits, procedures, or treatment. All patients met the *DSM-III* criteria for panic disorder or agoraphobia with panic attacks, none had any medical disorder, and none had received any medications besides aspirin and vitamins for at least 1 month. At intake, all patients received the Structured Clinical Interview for *DSM-III* (3), the Hamilton Rating Scale for Depression (4), the Zung Anxiety Scale (5), and the Beck Depression Inventory (6). They also donated blood for measurement of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG). Blood was taken after the patient had been in a sitting position for at least 1 hour; diet and exercise were not controlled. After the initial visit, the patient was offered 3 months of free treatment, either medication combined with self-programmed behavior therapy or behavior therapy alone. None of the patients selected behavior therapy alone. After 3 months, each patient was financially screened and asked to pay the minimum clinic fee of \$5.00 if possible. Four to 8 months after the initial visit, the patient was asked to attend a follow-up visit, at which time the Hamilton, Zung, and Beck scales were administered again and urine and blood were donated. Twenty-four (86%) of the 28 patients agreed to be restudied; two patients had moved from the city, and two declined to be reinterviewed. Free plasma MHPG was assayed according to a variation of the high performance liquid chromatography method of Scheinin et al. (7). The plasma was stored at -80°C until assayed.

RESULTS

After the initial visits, six of the 28 patients declined any treatment. A further six dropped out of treatment within 2 weeks, and four more dropped out within 6

Received Jan. 26, 1988; revised July 22, 1988; accepted Sept. 1, 1988. From the General Adult Clinic, University of Texas Mental Sciences Institute, Houston. Address reprint requests to Dr. Edlund, Department of Psychiatry, Rhode Island Hospital, APC Bldg., 9th Floor, 593 Eddy St., Providence, RI 02903.

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TABLE 1. Characteristics of Panic Patients Who Received Treatment or Declined or Dropped Out of Treatment

Variable	Treated (N=12)		Untreated (N=12)	
	Mean	SD	Mean	SD
Age (years)	34.6	8.6	39.0	9.7
Rating scale score				
Zung Anxiety Scale				
Pretreatment	45.3	7.5	38.8	9.1
Posttreatment	37.2	7.8	38.1	7.2
Hamilton depression scale				
Pretreatment	14.9	4.6	11.9	6.7
Posttreatment	5.3 ^a	2.8	9.1 ^a	3.6
Beck Depression Inventory				
Pretreatment	16.0	8.6	12.1	7.5
Posttreatment	10.9	8.5	12.3	7.0
Panic attacks per week				
Pretreatment	2.3	2.5	1.0	0.8
Posttreatment	0.3	0.6	0.7	0.8
Plasma MHPG level (pmol/ml)				
Pretreatment	15.3 ^b	4.3	20.1 ^b	5.8
Posttreatment	16.9 ^c	3.9	24.0 ^c	7.5

^aSignificant difference between groups ($t=2.9$, $df=23$, $p<0.05$).^bSignificant difference between groups ($t=2.3$, $df=23$, $p<0.05$).^cSignificant difference between groups ($t=2.9$, $df=23$, $p<0.01$).

weeks. At follow-up (mean=6.8 months), 12 of the 24 patients who agreed to be restudied were continuing in treatment and coming to the clinic at least monthly, and 12 were not in treatment. All of the 12 continuing in treatment were taking medication; 11 were taking alprazolam in doses of 0.25-6.00 mg/day, and one patient was taking desipramine, 200 mg/day.

We hypothesized that the patients who continued in treatment would have scores on the subjective and objective symptom scales which indicated more pretreatment panic attacks and more anxiety and depressive symptoms. Although the group continuing in treatment did have slightly worse symptom profiles at baseline, none of these differences was statistically significant (see table 1). Even at follow-up, the only statistically significant difference in symptom score between the two groups involved the posttreatment Hamilton depression score (see table 1). However, the patients who were continuing in treatment had a significantly lower initial mean MHPG level than those not continuing in treatment. (Their MHPG level was also lower at follow-up but may have been affected by treatment.) The hypothesis was not supported—the two groups did not differ statistically with regard to symptom measures—but there was a difference in MHPG, one of the variables the study intended to examine longitudinally.

DISCUSSION

It could be hypothesized that the subjects who continued in treatment did in fact feel more symptomatic than those who declined or dropped out of treatment

and that the symptom scales we used simply were not sensitive enough or did not test the nature of the symptoms which caused the patients to continue treatment. In fact, the patients who continued in treatment had higher scores on the symptom measures, although none of the differences reached statistical significance. It could also be hypothesized that some concomitant of low MHPG causes people to continue in treatment and that this MHPG-associated factor(s) is responsive to medication. However, there was no significant difference between the pre- and posttreatment MHPG levels in either group, and although the symptoms of the treated group did improve, there were no significant differences between the groups at the beginning of the study. While it is true that with a larger group there might have been significant symptomatic differences between the patients continuing and not continuing in treatment, the fact remains that plasma MHPG was more sensitive than the clinical measurements in distinguishing between groups.

Regardless of whether the symptom measures were insufficiently sensitive to note differences between the groups or whether a low initial MHPG level is directly or indirectly related to continuation in treatment, the result regarding selection bias is the same: our patients appeared to self-select for continuation in treatment on the basis of the biochemical variable that was the intended object of study. That such a selection bias would operate for a biochemical variable and not for clinical symptoms is not intuitively obvious.

The implication of this finding is that panic patients who elect to continue in treatment may be different, in biochemical terms, from those who do not continue in treatment. A corollary is that in biological studies of panic disorder, and perhaps other psychiatric disorders, subjects' initial volunteering for treatment may produce selection bias for biological variables that are the object of study, even when the clinical factors in different groups appear to be similar. Also, in this study continuing in treatment itself resulted in volunteer bias. Regardless of whether future studies find a volunteer bias affecting plasma MHPG levels in panic patients, the theoretical possibility always exists that volunteer bias may affect the biological results of clinical trials.

How can one avoid this problem? To some extent, volunteer bias is unavoidable—if people absolutely refuse to be studied, it is hard to compare them with those who agree. However, certain guidelines can be followed to minimize the difficulty. First, response rates of over 80% tend to keep the statistical effects of volunteer bias to a minimum (8). Second, one can attempt to later study nonrespondents. It is sometimes possible to sample at least a group of nonrespondents and to see whether they differ from the study group on variables of interest. Third and perhaps most important, one should remain cautious in generalizing the results of patient studies, such as clinical trials, to the entire universe of patients suffering from a disorder.

Patients undergoing clinical trials may well have

self-selected themselves for just those variables that are the objects of study. Standard measures of statistical inference demand a level of homogeneity for subjects that is sometimes difficult to achieve in human populations (8). Volunteers are often different from nonvolunteers. The ways in which they differ are frequently unknown and difficult to predict, and even following the best and most stringent experimental procedures may not obliterate the effects of volunteer bias.

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Ventricle-Brain Ratio and Alogia in 19 Young Patients With Chronic Negative and Positive Schizophrenia

Massimo Moscarelli, M.D., Bruno Mario Cesana, M.D., Silvio Ciussani, M.D.,
Nicoletta Calchi Novati, M.D., and Carlo Lorenzo Cazzullo, M.D.

In a group of 19 young patients with chronic mixed (both negative and positive) schizophrenia, the authors found that alogia was the only symptom to show a significant relationship to ventricle-brain ratio.

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The studies of Johnstone et al. (1), which revealed ventricular enlargement in some schizophrenic patients, have led to the hypothesis that two distinct schizophrenic syndromes may exist (2). One type is characterized by normal ventricles, a good response to neuroleptic drugs, and a predominance of positive symptoms. The second type is characterized by enlarged ventricles, structural brain damage, a lack of response to neuroleptics, and a predominance of negative symptoms.

Goetz and van Kammen (3), describing the relationship between symptoms and the ventricle-brain ratio (VBR) in their review of structural abnormalities in schizophrenia, said, "Studies seem to indicate that the subgroup of patients with brain atrophy are distinguishable both by lack of positive symptoms and by a particular predominance of negative symptoms."

In our clinical experience (4), the majority of schizophrenic patients are diagnosed as having mixed (both positive and negative) schizophrenia. The availability of more systematic measurements using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (5) has allowed us to evaluate whether ventricular enlargement is associated with the negative syndrome itself (a lack of positive symptoms and a predominance of negative symptoms) or only with a single negative symptom. In this latter case, the presence or absence of positive symptoms would not be relevant to ventricular enlargement.

We studied the relationship between individual positive and negative symptoms and VBR in a group of 19 young patients with chronic mixed schizophrenia.

METHOD

Our subjects were drawn from a group of patients consecutively admitted to the Institute of Clinical Psychiatry in Milan. Nineteen of the patients (14 men and five women) who were diagnosed according to *DSM-III* as having chronic schizophrenia and who were also identified as having mixed schizophrenia according to Andreasen and Olsen's criteria (5) were included in the study. The patients' mean \pm SD age was 29.2 ± 4.6 years, and none of them had an organic disease, drug addiction, or mental insufficiency.

The patients' mean \pm SD age at onset of illness was 18.6 ± 3.4 years, and their mean age at first hospitalization was 21.4 ± 4.8 years. Their mean number of hospital admissions was 11.4 ± 12.9 , and the mean total duration of their hospitalizations was 265.3 ± 268.6 days. They had attended school for a mean of 7.7 ± 2.9 years. Fifteen (79%) were unemployed, two (11%) were intermittently employed, one (5%) was employed, and one (5%) was a student.

The interviewer (M.M.) who administered the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms was blind to the patients' diagnoses. The values for the interrater reliability of both scales have been described elsewhere (4). Interviews took place during the first week of hospitalization, and scores were assigned only on the basis of these interviews. All of the patients were being treated with neuroleptics, and none had ever received ECT.

The global ratings of each symptom in each scale were related to VBR values. We also related to VBR values the individual symptom of inappropriate affect (included in the affective flattening item on the Scale for the Assessment of Negative Symptoms), which correlated more significantly with positive symptoms (4).

CT scans of the head were obtained without contrast by means of an EMI CT 1010 scanner. Scanned slices were 10-14 mm thick. The cut displaying the lateral ventricles was used to measure VBR by means of manual planimetry. A quantitative index was obtained by taking the ratio between ventricular and intracranial areas and multiplying by 100. Two raters blindly evaluated VBR, and the mean was used for

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statistical analysis. The interrater reliability was excellent ($r=0.98$, $p<0.001$).

We used a control group of 23 subjects whose only symptom was headache revealed by CT scan not to be organically based. This group included 17 men and six women; their mean \pm SD age was 25.8 ± 7.7 years.

The significance of the difference between patients and control subjects was assessed by using the chi-square test or analysis of variance (ANOVA). The relationship between VBR and other variables was investigated by simple regression analysis. Taking into account the number of patients and the distribution of the variables, we calculated nonparametric coefficients of correlation. The results of these calculations were always consistent.

RESULTS

There was no significant difference between the patients and the control subjects in sex ($\chi^2=0.1127$, $df=1$, $p=0.7370$) or age ($F=2.23$, $df=1$, 40 , $p=0.1432$).

The schizophrenic patients had a significantly higher mean VBR than control subjects: 5.1 ± 2.6 versus 3.4 ± 1.7 ($F=7.51$, $df=1$, 40 , $p=0.0091$).

None of the patients' sociodemographic characteristics was related to VBR. Alogia was the only one of the symptoms listed on either the Scale for the Assessment of Negative Symptoms or the Scale for the Assessment of Positive Symptoms for which the global rating was significantly related positively to VBR. The slope of the regression line was 0.9533 ($t=2.846$, $df=17$, $p=0.0112$; $r=0.5681$, $p=0.0056$).

The symptom of inappropriate affect seemed to have an inverse but not significant association with VBR. The slope of the regression line was -0.4376 ($t=-1.009$, $df=17$, $p=0.3269$; $r=-0.2378$, $p=0.1634$). In the majority of subjects its presence was due to "risus ephrenicus." Alogia scores and inappropriate affect scores are shown in table 1.

DISCUSSION

Unlike the other results of our study, which confirm results already published in the literature, the significant relationship between alogia and VBR has not been previously reported, to our knowledge. This may be because in the majority of our patients, the high alogia scores (scores of 4 and 5) were determined by the poverty of content of speech item, which is not included in some rating scales. When it has been included, it has been described as infrequent (reported in a personal communication by N.C. Andreasen in a group of 18 patients with mixed schizophrenia) or absent (6).

It should be borne in mind that poverty of content of speech and poverty of speech were the only two thought, language, and communication symptoms that distinguished schizophrenic patients from depressive and manic patients (7). Furthermore, in 1930 K. Kleist,

TABLE 1. Ventricle-Brain Ratios (VBRs), Scores for Alogia, and Scores for Inappropriate Affect of 19 Young Patients With Chronic Mixed (Negative and Positive) Schizophrenia

Patient	VBR	Alogia Score ^a	Inappropriate Affect Score ^a
1	2.01	1	0
2	2.18	0	2
3	2.36	1	1
4	2.42	3	4
5	2.75	3	1
6	2.96	4	4
7	3.21	0	3
8	3.71	3	0
9	4.50	3	0
10	4.82	4	4
11	5.65	3	3
12	5.71	5	1
13	6.03	5	3
14	6.22	4	1
15	6.52	5	1
16	6.81	4	1
17	7.53	4	0
18	8.92	3	1
19	11.90	4	1

^aFrom the Scale for the Assessment of Negative Symptoms (5); the symptom of inappropriate affect, however, correlated more significantly with positive symptoms (4).

translated in Cutting and Shepherd (8), described the allogical disturbance of thought (*alogische denkstörung*), characterized by a "lack of productivity of thought and by an incapacity to carry through a chain of thought." According to Kleist, "There is no doubt that the allogical thought disorders which occur in fore-brain injury match closely those that occur in schizophrenia, particularly the hebephrenic variety."

The research that has led to our highlighting a relationship between alogia and VBR would need to be confirmed by further studies taking into account the transcultural reliability of alogia, the presence of this symptom in other diagnostic groups, and the effects of pharmacological treatment on patients with alogia.

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Autoimmune Thyroiditis and Panic Disorder

Murray B. Stein, M.D., F.R.C.P.(C), and Thomas W. Uhde, M.D.

Contrary to reports on depression, the prevalence of antithyroid antibodies was not significantly higher in 38 patients with panic disorder than in 38 matched control subjects. Autoimmune thyroiditis is not commonly associated with panic disorder but may play a role in some specific clinical circumstances.

(Am J Psychiatry 1989; 146:259–260)

Panic disorder may be associated with a variety of medical conditions (1). Among these, a relationship between panic disorder and thyroid disease seems to stand out as a particularly intriguing possibility (1), although the evidence for such an association remains inconclusive. Studies of peripheral thyroid indexes have generally failed to find either significantly higher or significantly lower values in patients with panic disorder than in normal control subjects (2), but patients with panic disorder have been reported to have lower thyrotropin (TSH) responses to thyrotropin-releasing hormone (TRH) than normal control subjects (3), a finding consistently reported in approximately 25% of depressed patients (4).

Because panic disorder and major depression share many clinical and biological characteristics (5), we felt it would be worthwhile to further identify potential etiopathologic similarities and differences between the two disorders. In addition to abnormalities in TSH response to TRH seen in depression (4), some patients with depression exhibit the presence of antithyroid antibodies (6, 7). The presence of antithyroid antibodies is suggestive of a diagnosis of "painless" or "silent" thyroiditis, a common thyroid disorder of presumed autoimmune origin (8). To our knowledge, no studies to date have systematically examined the prevalence of antithyroid antibodies in patients with panic disorder. In order to further define the role of thyroid abnormalities in panic disorder, and to further clarify the relationship between panic disorder and major depressive illness, we conducted a study of antithyroid antibodies in 38 patients with panic disorder and 38

age- and sex-matched normal control subjects. Sex-matching was particularly indicated, since autoimmune thyroiditis is more likely to affect women (8).

METHOD

We studied 38 patients (27 women and 11 men; mean \pm SD age, 36 ± 8 years) who met *DSM-III-R* criteria for panic disorder and 38 healthy control subjects (27 women and 11 men; mean \pm SD age, 33 ± 11 years). All subjects were interviewed by a research psychiatrist with the aid of a semistructured interview derived from the Schedule for Affective Disorders and Schizophrenia—Lifetime Version. All patients met *DSM-III-R* criteria for panic disorder, and none met current criteria for a major depressive episode. All control subjects were free of any past or present *DSM-III-R* axis I diagnosis.

All subjects were medication free for a minimum of 3 weeks before the study began and were determined to be medically healthy on the basis of a complete physical examination, CBC, SMAC-20, urinalysis, ECG, and chest X-ray. Subjects with a history of thyroid disease were excluded from the study. All subjects gave informed, written consent to participate in this study after a thorough explanation of the procedures by one of us. Titers of antimicrosomal antibodies were measured by immunofluorescence and indirect hemagglutination techniques (Bio-Science Labs), and titers of antithyroglobulin antibodies were measured by the tanned red cell method (Bio-Science Labs). Antimicrosomal antibody titers of 1:100 or greater were considered positive, as were antithyroglobulin antibody titers of 1:10 or greater.

The proportion of patients and control subjects with or without antithyroid antibodies was compared by using Fisher's exact test. A one-tailed test was used to examine the hypothesis that panic disorder patients would have a higher prevalence of antithyroid antibodies than control subjects.

RESULTS

Four patients with panic disorder (10.5%) and two control subjects (5.3%) exhibited the presence of antithyroid antibodies (Fisher's exact test, one-tailed $p=0.34$). All six subjects with antithyroid antibodies were women; thus, four of 27 women with panic dis-

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The authors thank Drs. Thomas Mellman and Manuel Tancer. Copyright © 1989 American Psychiatric Association.

order (14.8%) and two of 27 healthy women (7.4%) had antithyroid antibodies (Fisher's exact test, one-tailed $p=0.33$).

Two women with panic disorder who had antithyroid antibodies continued under our care, thereby enabling us to document their titers serially over time. In both cases, their titers of antithyroid antibodies became undetectable within 6 months, and this time course did not closely parallel the course of their anxiety disorder.

DISCUSSION

We failed to find a higher prevalence of antithyroid antibodies among patients with panic disorder than among healthy control subjects. These preliminary findings are interesting in relation to reports by several independent research teams (6, 7) which suggested that patients with depression have a high rate of autoimmune thyroiditis.

Several factors must be considered in interpreting these findings. First, a cautionary note must be made regarding both our own negative findings and the previously published reports of autoimmune thyroiditis in patients with affective symptoms. The studies that found a high prevalence of antithyroid antibodies in depressed patients (6, 7) did not use a normal control group for comparison but instead relied on comparisons to population norms from other epidemiological surveys. Depending on the demographic characteristics of the individuals in each study, this may or may not be a valid means of comparison. For example, whereas one study of depressed patients (7) interpreted a prevalence of antithyroid antibodies of 20% compared to a general population estimate of 5%–10% as reflecting an increase, our rate of 10% in panic disorder patients was not significantly different from the rate of 5.3% in our normal control group. Therefore, confirmation of the importance of antithyroid antibodies in depression awaits further replication and the use of a normal control group. Furthermore, most studies of antithyroid antibodies in depression (6, 7) have examined heterogeneous groups of individuals with depressive symptoms and not exclusively individuals meeting rigid criteria (e.g., *DSM-III-R*) for a well-defined major depressive disorder. Had we chosen to study individuals with anxious symptoms, rather than those with carefully diagnosed *DSM-III-R* panic disorder, our results might have more closely resembled the findings reported for depression. Thus, differences in methodology preclude direct comparison of our findings to those for depression and should not be taken as evidence which suggests that

panic disorder and major depression differ in their propensity for an association with underlying autoimmune thyroiditis.

Do our findings imply that autoimmune thyroiditis plays no role in patients with panic disorder? While our study indicates that active autoimmune thyroiditis is not an intrinsic biological substrate of panic disorder, intriguing possibilities remain regarding the exact relationship between some patients with panic attacks and autoimmune thyroid dysfunction. Our observation that antithyroid antibody titers may diminish and eventually become undetectable over time demonstrates that our study is merely a cross-sectional assessment of these titers at a given point in time. Conceivably, the onset of the painless hyperthyroid phase of autoimmune thyroiditis (8) could initiate or exacerbate panic attacks in susceptible individuals, and the eventual disappearance of antithyroid antibodies in some cases could make detection and diagnosis at a later time impossible. Also, autoimmune thyroiditis is frequently seen to wane during pregnancy and then wax in the postpartum period (9); of interest, this course parallels the pattern of many women with panic disorder who experience remission of their symptoms during pregnancy and recurrence in the postpartum period (10). Whether or not autoimmune thyroiditis plays a role in this pregnancy-related fluctuation in symptoms often seen in panic disorder deserves further testing in longitudinal studies.

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DSM-III Subclassification of Dissociative Disorders Applied to Psychiatric Outpatients in India

Shekhar Saxena, M.D., and K.V.S.R. Prasad, M.B.B.S.

In subclassifying 62 cases of DSM-III dissociative disorders in India, the authors found that 56 (90.3%) fell into the atypical subcategory. These cases could be easily separated into two additional subcategories, simple dissociative disorder and possession disorder, by using specified diagnostic criteria.

(Am J Psychiatry 1989; 146:261-262)

Dissociative phenomena were major areas of clinical investigation during the time of Janet (1) and Freud (2). Subsequently, there has been a decline of interest in these clinical syndromes, although there has been no evidence to suggest that the incidence of these phenomena has in any way diminished since that time (3).

DSM-III separated dissociative disorders from the other manifestations of hysteria and gave them an independent identity. It also delineated a few better-defined entities (psychogenic amnesia, psychogenic fugue, multiple personality, and depersonalization disorder) and gave them the status of specific subcategories. However, a wide range of other dissociative phenomena are seen all over the world, and they need to be better described and incorporated into classification systems (4).

One of our earlier studies (5) reported on the difficulties encountered in assigning DSM-III dissociative disorder subcategories to Indian patients diagnosed as having hysteria according to ICD-9. The description and tentative diagnostic criteria for the suggested new entity of simple dissociative disorder have also been reported (6).

In this paper we wish to present further data on the clinical characteristics and subclassification of dissociative disorders seen in a psychiatric outpatient service in India.

METHOD

Case records of all of the 2,651 patients seen in the adult psychiatric outpatient clinic of the All-India Institute of Medical Sciences Hospital during the year 1986 were screened for the presence of dissociative symptoms. Dissociative symptoms were defined according to the DSM-III description (sudden, temporary alteration in the normally integrative functions of consciousness, identity, reality, or motor behavior). After we excluded case records with inadequate information, there were 62 cases that fitted into the dissociative disorders category of DSM-III. This was 2.3% of the total outpatient cases screened. The records of these 62 cases were reviewed jointly by us, and the relevant sociodemographic and clinical data were collected. Diagnoses of subcategories of dissociative disorders were made on the basis of the criteria given in DSM-III. In addition, atypical dissociative disorder was further subdivided into simple dissociative disorder, on the basis of criteria suggested by Saxena (6), and possession disorder, on the basis of criteria proposed by Yap (7). The operational criteria used for defining these subcategories are as follows:

Simple dissociative disorder. 1) Short periods (a few minutes to a few hours) of alteration in consciousness manifested by relative unresponsiveness to the external environment and painful stimuli; 2) sudden onset and termination; 3) partial or complete amnesia for events that occurred during the period of alteration in consciousness; 4) disturbance not due to an organic mental disorder; 5) associated features: motor movements of the body that may resemble generalized epileptic convulsions or may be bizarre and crying, shouting, or verbalizing thoughts that may be completely at variance with the usual characteristics of the person's personality.

Possession disorder. 1) Short periods (a few minutes to a few hours) of change in the person's identity manifested by change in voice, mannerisms, and behavior—the new identity may be of a known person already dead or of a culturally accepted spirit, demon, god, or mythical figure; 2) sudden onset and termination; 3) partial or complete amnesia for the new identity and events that occurred during the possession episode; 4) disturbance not due to an organic mental disorder; 5) associated features: attention seeking and

Received Jan. 13, 1988; revision received July 18, 1988; accepted Aug. 31, 1988. From the Department of Psychiatry, All-India Institute of Medical Sciences, New Delhi. Address reprint requests to Dr. Saxena, Addiction Research Unit, Institute of Psychiatry, 101 Denmark Hill, London SE5 8AF, England.

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TABLE 1. Diagnostic Subcategories of 62 Indian Patients With DSM-III Dissociative Disorders

Subcategory	N	%	Confidence Interval (95% level)
Psychogenic amnesia	0	0	
Psychogenic fugue	4	6.5	0.21–12.69
Multiple personality	0	0	
Depersonalization disorder	2	3.2	0–7.73
Atypical dissociative disorder	56	90.3	82.81–97.82
Simple dissociative disorder ^a	50	80.6	
Possession disorder ^a	6	9.7	

^aSuggested new subcategory for DSM-III atypical dissociative disorder.

dramatizing behavior during the possession episode—may occur during religious ceremonies.

RESULTS

Of the total of 62 patients, 19 (30.6%) were 20 years of age or younger, 27 (43.5%) were 21–35 years old, and 16 (25.8%) were over 35 years of age. Thirteen (21.0%) were male and 49 (79.0%) were female. Forty-two (67.7%) were married; 37 (59.7%) were housewives. Twelve (19.4%) of the patients were illiterate, but seven (11.3%) had a college education.

On the basis of the DSM-III description, there were disturbances of consciousness in 53 (85.5%) of the cases, of identity in 10 (16.1%), of reality in two (3.2%), and of motor behavior in 24 (38.7%). The total duration of symptoms was less than 1 year in 35 (56.5%) of the cases. The average duration of each episode was less than five minutes in 11 (17.7%) of the cases, 5–60 minutes in 36 (58.1%), and 1–4 hours in 10 (16.1%). The average duration exceeded 4 hours in only five cases (8.1%), in which two patients were diagnosed as having depersonalization disorder and three as experiencing psychogenic fugue.

DSM-III subcategories for the 62 patients are given in table 1.

DISCUSSION

This study was based on DSM-III diagnoses; however, the results may be equally relevant to DSM-III-R,

as the criteria for dissociative disorders have not undergone any major changes. The subcategory of atypical dissociative disorder has been replaced by dissociative disorders not otherwise specified, and more examples have been included; however, these still do not cover the dissociative phenomena observed in this study.

The DSM-III description of the general characteristics of the dissociative disorders seems satisfactory; it covers the whole range of functional alterations in consciousness, identity, reality, and motor behavior, although the last-named has been excluded from DSM-III-R. However, the finding that more than 90% of the cases in this study had to be assigned to the atypical subcategory suggests that the subcategorization of dissociative disorders is not comprehensive enough. Cases described here as simple dissociative disorder and possession disorder are probably encountered in most parts of the world, although they may be more common in the developing countries. We suggest that the criteria used in this study be applied by other clinicians in order to demonstrate the descriptive validity, or the lack of it, of these two syndromes. In the meantime the brief descriptions of the symptoms of simple dissociative disorder and possession disorder that we have given need to be included in future revisions of DSM as examples of dissociative disorder not otherwise specified.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

TWO VIEWS OF THE 1988 REVIEW OF PSYCHIATRY

American Psychiatric Press Review of Psychiatry, vol. 7, edited by Allen J. Frances, M.D., and Robert E. Hales, M.D. Washington, D.C., American Psychiatric Press, 1988, 673 pp., \$49.95.

This volume continues the tradition of providing excellent, up-to-date reviews on subjects of interest in the field of psychiatry. This is the fourth volume produced under the editorial leadership of Allen Frances and Robert Hales, who are to be commended for their outstanding contributions in this as well as earlier reviews. Like the earlier annual reviews, this volume is sizable and includes five sections, each containing five to seven chapters with a foreword and an afterword provided by section editors. The selection of topics this year is eclectic but fully representative of the wide range of interests covered by psychiatry. The five sections are Panic Disorder, edited by David H. Barlow and M. Katherine Shear; Unipolar Depression, edited by Martin B. Keller; Suicide, edited by J. John Mann and Michael Stanley; Electroconvulsive Therapy, edited by Robert M. Rose and Harold Alan Pincus; and Cognitive Therapy, edited by A. John Rush and Aaron T. Beck. Although the list of section editors itself is impressive (all are noted experts in their respective areas), the list of contributors to the individual chapters is equally impressive, including 44 additional experts from a variety of theoretical backgrounds.

As an example, the section on suicide begins with a foreword by the section editors setting the stage for the following six chapters. Lee Robins and Pamela Kulbok provide an exhaustive review of the retrospective and prospective studies of the epidemiology of suicide, including a review of studies based on death certificates. Robert Hirschfeld and Lucy Davidson report on risk factors for suicide, including data from both general and psychiatric populations and data on suicide among medical and surgical patients. They also report on how alcohol interacts with suicidal behavior and how those who attempt suicide differ from those who actually kill themselves. Michael Stanley and J. John Mann, who have added so much to our knowledge of biological factors associated with suicide, report on postmortem findings in suicide victims, CSF studies of suicide attempters, and neuroendocrine and hormonal studies of suicide and suicidal behavior. David Brent, David Kupfer, Evelyn Brommelt, and Mary Amanda Dew provide a change of focus in addressing both assessment and treatment of patients at risk for suicide. They cover the gamut of problems, from assessment of suicidality to psychiatric hospitalization to somatic and pharmacological treatments. Cynthia Pfeffer, who has recently emerged as the maven of child and adolescent suicidal behavior, adds her expertise in risk identification and intervention in this population. Her recommendations are made with care and show her genuine concern for patients. The last chapter, about the prevention of suicide, is written by George Murphy, who has made a career of educating us about suicide. Murphy's work

is always a delight to read, and this contribution is no exception. He tackles the difficult question of whether suicide can be predicted as well as the more urgent question of whether suicide can be prevented. Murphy also comments on the physician's role in preventing suicide and shows the steps that we can take to prevent suicide. The overlap among these six chapters has been kept to a minimum by the section editors, who are to be commended for their efforts. Overall, the section is highly readable, provides up-to-date and thoughtful information, and yet is not so lengthy as to intimidate the typical clinician.

Now that this volume has been produced, we will eagerly await volume 8. It promises to be interesting because it will focus on borderline personality disorder, child psychiatry, alcoholism, psychiatry and the law, and difficult situations in clinical practice.

DONALD W. BLACK, M.D.
Iowa City, Iowa

American Psychiatric Press Review of Psychiatry, vol. 7, edited by Allen J. Frances, M.D., and Robert E. Hales, M.D. Washington, D.C., American Psychiatric Press, 1988, 673 pp., \$49.95.

This seventh volume of a justly popular series is organized about special teaching sessions at APA's annual meeting. The topics chosen are of great interest to practitioners, who should appreciate this very current material.

The editors have been helped by leading figures who have notably contributed to scientific psychiatry, and they succeed in teaching their colleagues as well. The writing is always good and often lively and interesting. Allen Frances and Robert Hales should be congratulated on their efforts and accomplishments.

Are there no caveats? Unfortunately, yes. It should be realized that this is a collection of "minitextbooks," not journal articles. What's the difference? The difference is that these articles have not undergone the tedious but rigorous process of peer review—although they have the benefits of their section editors. There are factual misstatements that would have been winnowed out by peer review, although probably no more than in the usual textbook. Of more concern are the evaluative summary articles concerning the efficacy of cognitive-behavioral treatment of panic, the psychotherapeutic treatment of depression, and the review of empirical studies of cognitive therapy.

Psychiatry now aspires to the elevated status of a clinical science. We are no longer content with the dogmatic statements of revered authorities. The controlled, comparative, randomized clinical trial has become the gold standard as we progress from How to do it to the logically previous question of Should we do it?

Unfortunately, these sections do not help readers deal with the conceptual pitfalls they must be wary of in order to eval-

uate clinical trials. Judging the evidence produced by clinical trials is not a simple matter. Because of the heterogeneity of psychiatric illness, differences in outcome are often attributable to fluctuations in sample composition that are not obviated even by using *DSM-III-R* criteria.

If one accepts medication as a standard of efficacious treatment and wishes to establish the relative merits of psychotherapy, it seems simple just to compare two groups—one given medication and one given psychotherapy. Unfortunately, this strategy fails because medication is frequently ineffective and patients often spontaneously remit. It is no great trick to select a sample of moderately ill outpatients for whom medication is no better or even worse than placebo, despite nominal diagnoses. Therefore, such studies need an internal calibration—a demonstration that, in this particular sample, medication was shown to be efficacious by superiority to a concurrent control placebo condition.

Only if that is done can there be meaningful comparisons between medication and psychotherapy, as well as the creation of the choice of contrasting psychotherapy with the control nonspecific condition. Plainly, if a psychotherapy is no better than placebo plus 15 minutes of nondirective, nonspecific support, it does not warrant much practical attention.

These elementary points regarding the design and interpretation of comparative clinical trials are not explained to the reader. Instruction on this point would have made it clear that the overwhelming preponderance of the psychotherapy versus pharmacotherapy literature fails to observe this methodological necessity. This fallacy also casts light on the remarkably minor benefits demonstrated in studies of the combination of pharmacotherapy and psychotherapy compared with psychotherapy alone. This lack of incremental benefit would not be surprising in samples in which pharmacotherapy was ineffective.

The National Institute of Mental Health (NIMH) Collaborative Research Program on the Treatment of Depression wisely incorporated this methodological necessity. Their long-awaited peer-reviewed publications are still in the offing, but there have been presentations indicating that when their sample was split into more and less disabled patients, the 60% with less disability derived no more benefit from medication than they did from placebo plus case management (nor were the psychotherapies superior to the control condition). The statistical interpretation of the other 40% is still being debated, but it seems clear that the rank ordering of benefit is 1) medication, 2) both psychotherapies, and 3) the control condition or placebo. Therefore, our concern with internal placebo calibration is realistic and not academic. This important NIMH study is alluded to only once in the *Annual Review*, and the negative psychotherapy results are attributed to therapist inadequacy (shades of psychoanalysis).

The substance of these evaluative reviews consists almost entirely of flawed studies. They do not establish the efficacy of psychotherapy but may depend on the limited range of efficacy of antidepressant medication, combined with the high rate of spontaneous remission in mild disorders, which produces a misleading impression.

Further, in these reviews, trials of very dubious quality, such as those entirely dependent on mailed questionnaires of an uncertain date, are treated as if they were entirely equivalent to the most rigorous clinical assessment.

What can be done about this? Peer review is the best answer but would entail both delay and expense. A useful alternative is to make sure that in controversial areas the controversy is fairly presented. It is probably asking too much that the participants in a debate should unbiasedly present

the opposing viewpoints. Therefore, it is incumbent on the editors to ensure that all the protagonists have their say. This is most crucial when presenting data relevant to comparative treatment efficacy.

As experience at the APA annual meeting has shown, debate is both desirable and engaging to the audience. This feature should be incorporated into this series, which would make these volumes even more valuable additions to your library.

DONALD F. KLEIN, M.D.
New York, N.Y.

TEXTBOOKS

American Psychiatric Glossary, 6th ed., compiled and edited by Evelyn M. Stone. Washington, D.C., American Psychiatric Press, 1988, 143 pp., \$19.95; \$9.95 (paper).

Did you know that lethologica is the temporary inability to remember a proper noun or name? I was relieved to discover a name for this condition, which increasingly plagues my existence, even though I probably won't remember it for long. I found this word after a serious look at the *American Psychiatric Glossary*.

The *Glossary* makes no pretense of being a comprehensive dictionary whose forbidding demeanor would discourage all but the supremely motivated seeker of a definition. Instead, it is compact yet accurate, with easy-to-read type fonts and page composition, almost asking the reader to browse.

The *Glossary* proper ends at page 110. It is followed by a list of abbreviations and seven helpful tables. Among the abbreviations, even TM (transcendental meditation), Maharishi Mahesh Yogi's commercial repackaging of plain vanilla meditation, appears. The definitions are almost all clear, concise, and cross-referenced with other terms. New technologies are properly defined, including PET (positron emission tomography), CAT (computerized axial tomography), and MRI (magnetic resonance imaging). So is DRG (diagnostic related group). In the first table, drugs of abuse are cataloged by pharmacological families and then paired up with their street names, those dark additions to American slang.

In the *Glossary* proper, one of the few definitions that is too brief is for crack—"freebase or alkaloidal cocaine." This definition could leave the reader puzzled about "freebase" and "alkaloidal" and gives no hint that this variety of cocaine can be smoked. The term "neurosis" is maintained from its *DSM-II* glory days. Definitions of varieties of neurosis, neurotic disorder, and neurotic process march in quick succession. Psychoanalytic terms abound, even the "Wednesday Evening Society," the group of Freud's original followers. "*Zeitgeist*" is here too, perhaps because Goethe is credited with originating the word and Freud won the Goethe Prize or so "zygosity" would not be alone in the Z section.

Poor "zyosity." Along with many other words, it is not defined in the *Glossary* proper; instead you are referred to the Table of Research Terms in the back. There it is defined in what is actually one of three separate, small-print "mini-glossaries" for forensic, research, and neurological terms. The total content of these tables is substantial, and they contain such important terms as the "right to refuse treatment," "confabulation," and "control group."

When the 1990s bring around the seventh edition, I suggest an end to the lexicographic apartheid that sent about

100 different terms to their own small-print "homelands." Not all, like "zygosity," leave a forwarding address. I also favor affirmative action to ensure that terms of increasing modern significance like "neuropeptide" and "dexamethasone suppression test" get into the book (DST does appear in the table of abbreviations, however).

Although a glossary is a dictionary of technical terms, some of this *Glossary's* entries are descriptions of organizations or "minibiographies" of psychiatrists and psychoanalysts, making it into a "micro-encyclopedia." Another suggestion: these could be moved to tables in the back of the book to replace the tables no longer there if terms from forensics, research, and neurology were sent to the main glossary for an equal place in the sun.

The book ends with the Table of Schools of Psychiatry, identifying founding fathers or mothers of each school. More properly, this is a table of theories of personality and psychotherapy, with Freud at the top. My final vote for the 1990s would encourage some revision here: quietly drop references to Wilhelm Reich's orgone therapy, give Buddha (instead of Alan Watts) credit for Zen, and put in Hans Kohut (assuming he will still be popular).

This sixth edition of the *Glossary* will probably sell many copies; more than 400,000 are traditionally printed for each edition. In addition to psychiatry students, it will be of great interest to the professions of nursing, law, and other mental health disciplines and to interested lay people. As a practicing psychiatrist, I learned some new terms just flipping through the pages, and I got some insights into the state of our discipline.

This is indeed an American psychiatric glossary, much as Oxford publishes separate dictionaries for the United States and the United Kingdom. It reflects the depth of a Freudian tradition that never really took hold in Europe, the scourge of drug abuse, and the interest Americans have in our profession (each edition produces one *Glossary* for every 500 Americans).

JOHN HOCHMAN, M.D.
Tarzana, Calif.

Psychiatry for the House Officer, 3rd ed., by David A. Tomb, M.D. Baltimore, Williams & Wilkins Co., 1988, 236 pp., \$14.95 (paper).

This is the third edition of what has been a very successful book for Dr. David Tomb of the University of Utah. This slender book is part of Williams & Wilkins House Officer series, which provides a "bare bones" approach to medical illness. This is the sort of book that all house officers love to carry in their coat pockets so that when they encounter a troublesome situation they can immediately refer to their book and learn how to manage it. It may seem that this "cookbook" approach, so successful in internal medicine, would be difficult to use in psychiatry because psychiatric patients seem to be unique. Dr. Tomb shows that it is not only possible to use this approach but practical as well. He further demonstrates that a modest book can provide factual, detailed, and reliable advice.

I am a fan of this book and have been since its first edition was published in 1981. I now supervise residents and medical students on an adult inpatient unit. At the start of each rotation I advise the students to buy this book. I tell them, quite confidently, that if they read the book twice by the end of their 6-week rotation, they will know more psychiatry

than many practicing psychiatrists. I don't think this is an exaggeration; this small book is packed with information that is amazingly up-to-date. In fact, although this book came out in the spring of 1988 it includes among its many references papers that came out just before the book was published. Dr. Tomb has carefully culled the literature for papers that are relevant to clinical practice.

The book is well organized and accessible. It provides chapters on all the major psychiatric syndromes as well as on subjects not typically covered in most textbooks but useful to an on-call resident. Examples of the latter include "Grief and the Dying Patient" and "Psychiatric Symptoms of Nonpsychiatric Medications." Dr. Tomb also provides chapters that briefly review mental retardation, psychotherapy, biological therapies, the elderly patient, sleep disturbances, and, of course, psychiatric classification and assessment.

The structure of individual chapters is useful in that the most important information is highlighted. Important concepts are underlined, and specific instructions are numbered. References are included at the end of each chapter and kept mercifully brief but up-to-date in case the house officer should want additional information. Psychiatric jargon is minimized, a practice that writers of other texts would be smart to copy. Unfortunately, psychiatry tends to have its own language, which can make it inaccessible to the uninitiated. House officers early in their training do not need jargon. They need information to get their job done.

Nothing is perfect, and as much as I like this book, there are minor imperfections. These include typographical errors and errors in diction that should have been caught by the copy editor and occasional bits of information that are debatable. For example, Dr. Tomb states that mania requires 10 to 20 ECTs. In fact, in 1986 my associates and I found that manic patients required fewer ECTs than depressive patients (8.5 versus 9.0, on average) (1). Books like this tend to be successful because they minimize controversy. For teaching purposes, it is simpler to present topics in black and white terms. This is why students often think that the practice of medicine is simple. Experienced clinicians know that the areas of gray tend to overshadow those of white and black. Sometimes the information presented in this way seems a little too pat. This is a minor criticism, and not something that would keep me from highly recommending this book for medical students in their third-year clerkship and for young physicians beginning their residencies.

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DONALD W. BLACK, M.D.
Iowa City, Iowa

ETHICAL ISSUES

Murderous Science: Elimination by Scientific Selection of Jews, Gypsies, and Others, Germany 1933–1945, by Benno Müller-Hill; translated by George R. Fraser. New York, Oxford University Press, 1988, 208 pp., \$24.95.

The eugenics movement, based on a primitive and inaccurate understanding of human genetics, was a movement for

"race improvement," founded by the eminent nineteenth-century English geneticist Sir Francis Galton. It attempted "to anticipate the slow and stubborn process of natural selection, by endeavoring to breed out feeble constitutions and petty and ignoble instincts, and to breed in those which are vigorous and noble and social." It was this movement which promulgated the "scientific" basis of the racist ideology of Nazism, and it was not peculiarly German. On the contrary, and in view of the wide support this movement received in Europe and North America, the German experience must be viewed as a case study of the moral dangers that await public policy when it is derived solely from what appear to be obvious and overriding ideological and ethical implications of contemporary scientific perspectives. In this German experience, the academic disciplines and professions most directly involved in eugenic extermination programs were psychiatry, genetics, and anthropology.

In this devastatingly honest and painstakingly careful book, the German geneticist Benno Müller-Hill describes the intellectual and moral debasement, through this ideology, of the leaders of German universities, research institutes, and learned professions. The role of academic leaders in formulating policies and in actively participating in sterilization and in mass murder, initially of psychiatric patients and later of Jews and others, has not been previously detailed. In a series of intense and revealing interviews with many of the professionals involved, who continued in eminent positions, Professor Müller-Hill can detect no repentance or apologies. What he does find is a denial of awareness of complicity, even when he is able to document the actions of the subjects of his interviews. The prevarications, circumlocutions ("race hygiene," "euthanasia"), and denials amply demonstrate how continuously aware these people were that they were going far beyond any existing concept of human decency.

The policies of sterilization and murder of the chronically mentally ill had been advocated for a considerable time before the Nazis came to power, initially by professionals and academics. In 1920, a jurist, Professor Binding, and a psychiatrist, Professor Hoche, published a book entitled *The Sanctioning of the Destruction of Lives Unworthy To Be Lived* on euthanasia as a treatment for psychiatric illness. In 1933, 6 months after the Nazi rule began, the law for the "prevention of progeny with hereditary defects" was passed, allowing for compulsory sterilization in cases of "congenital mental defects, schizophrenia, manic-depressive psychosis, hereditary epilepsy, . . . and severe alcoholism." Prof. Ernst Rüdin, director of the Kaiser Wilhelm Institute of Psychiatry (now the Max Planck Institute) in Munich, who is properly known as the initiator of family studies in psychiatry, was an advocate of widespread sterilization to further "racial hygiene." Rüdin was one of three authors of the official textbook on implementing the sterilization laws for persons with hereditary illness and advocated an even wider compulsory sterilization, including "all who were socially inferior psychopaths . . . and the great mass of serious and incorrigible constitutional criminals." Franz Kallmann, whose father was a convert from Judaism and who was forced out of German academic life because of this, was a fellow of Professor Rüdin. When allowed to speak for the last time at a meeting in Germany, the International Congress of Population Problems in 1935, his talk included the following: "It is desirable to extend prevention of reproduction to relatives of schizophrenics who stand out because of minor anomalies, and, above all, to define each of them as being undesirable from the eugenic point of view at the beginning of their reproduc-

tive years." Kallmann later became an important founder of psychiatric genetics and human genetics in the United States.

The sterilization of psychiatric patients was ended in August 1939, and mass murder of patients was introduced by order of Hitler in September 1939; in his order he calls these murders "mercy killing." Following issuance of this order, all psychiatric hospitals in Germany were required to submit questionnaires on each patient. Based on 283,000 questionnaires, a committee of psychiatric experts determined who were suitable for being killed. At least 75,000 were transferred to and murdered in camps designed for mass killing. This was the first use of poison gas in mass murder. Following protests by the Catholic Church, these death camps were disbanded, but murder through deliberate neglect continued, including starvation, denial of heat in winter, and denial of medical care. In the Berlin district, only 2,000 out of 15,000 psychiatric inpatients survived the war. Medical and paramedical personnel who operated the killing institutions were transferred, following their closure, to the death camps where mass murder of Jews was carried out; there they were to select persons for murder and to operate the gassing installations.

In some psychiatric hospitals, including that at Buch in Berlin, "research wards" were established in which measurements were made on patients who were then sent for murder elsewhere. Brains were dissected and studied as part of the research project. (One such case was uncovered [1] in a collection of the brains of schizophrenic patients, the Vogt collection, following publication of anatomical examinations in the *Archives of General Psychiatry* in 1985.) Müller-Hill states that other collections from these murders still exist in Frankfurt and elsewhere.

The thorough debasement of German academicians and scientific institutions under Hitler is amazing. The German Research Society (Deutsche Forschungsgemeinschaft), a national body giving research grants (similar to the National Institute of Mental Health and the Alcohol, Drug Abuse, and Mental Health Administration), gave a grant in which the principal investigator was Prof. O. von Verschuer, director of the Kaiser Wilhelm Institute of Anthropology in Berlin-Dahlem and an extreme racist. His former postdoctoral fellow, Dr. Joseph Mengele, assisted him by providing blood, eye, and brain specimens from inmates at the Auschwitz concentration camp, whom Dr. Mengele selected for study and subsequent murder. In one instance, a series of twins and an entire family of eight were killed at his order by intracardiac injections so that their heterochromatic eyes could be sent to the Dahlem Institute. Although the deaths were described as due to an epidemic in the camp, a referee for the submitted manuscript suspected unnatural death. In 1949, despite the existence of a published description of Dr. Mengele's reputation for murderous activities at Auschwitz at the time of this "research," a committee of distinguished professors determined the following about Professor von Verschuer:

We cannot tell, from the evidence available to us, to what extent Dr. Mengele himself was aware of the abominations and murders perpetrated in Auschwitz during the period under discussion, that is when the blood samples were being sent We believe it would constitute a pharisaical attitude on our part if, in the light of the situation today, we were to consider a few isolated events of the past as marks of some unpardonable moral defect in a man who, in other respects, had honorably and courageously pursued his difficult path,

and who had often enough shown evidence of his high-minded character.

Verschuier, who died in 1969, became Professor of Human Genetics and director of an institute for human genetics at the University of Münster after World War II.

This story illustrates the most disturbing of Müller-Hill's findings: that the coverup, denial, and rationalizations that went on throughout the Nazi period also continued afterward, and nearly every participant found a way to avoid punishment. It is hard to believe that murderous racism will return, but surely there are other attractive ideologies that will corrupt the moral judgment of scientists. Perhaps this corruption will be less tempting for those who have an awareness of the slippery moral slope on which many German psychiatrists and geneticists foundered.

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ELLIOT S. GERSHON, M.D.
Bethesda, Md.

Ethical Issues in the Psychotherapies, by Martin Lakin. New York, Oxford University Press, 1988, 164 pp., \$24.95.

In this book, Martin Lakin, an experienced practitioner and teacher of psychotherapy at Duke University, undertakes to list and discuss the multiple ethical problems intertwined inextricably within the practice of psychotherapy. Some of these problems are obvious; some are subtle. His descriptions are based on findings from his own practice, a fairly extensive but somewhat spotty review of the relevant literature, and interviews with approximately 100 psychotherapists whose degrees of experience, theoretical interests, and practice approaches differed markedly.

Dr. Lakin's intention is to examine the impact of ethical issues from the points of view of psychotherapeutic technique and ideology. He starts off with a chapter based largely on vignettes supplied by the therapists he interviewed; these vignettes illustrate therapists' concerns about a wide variety of ethical problems encountered in their practices. It can be seen that most of these problems stem from the misuse or abuse of the power implicit in the role of the therapist. Important among them are the nontherapeutic imposition on the patient of the therapist's values and the use of the relationship for the satisfaction of financial, sexual, and psychopathological needs. These vignettes have considerable interest; they are concrete, specific, and down-to-earth, and they confirm the ubiquity of the thorny ethical dilemmas faced by psychotherapists in the hurly-burly of the psychotherapeutic encounter. I must say, however, that I was a bit startled at the very marked activity displayed by the therapists interviewed. In the situations described in this book, they were often taking authoritarian postures, giving advice, directing their patients or clients, and even making judgmental remarks. Maybe this is how most psychotherapists actually practice, and, if so, the observation is interesting; or it may be the result of some selection bias by the author in his sample.

Dr. Lakin then goes on to discuss what he calls the deterioration effects of unethical therapist behavior. This utilitarian emphasis, somewhat scanting the moral wrongness of the actions taken, is in line with the author's cool, objective,

and practical approach to his subject. The next four chapters deal more specifically with the ethical concerns faced in individual, group and dyadic, marital and family, and organizational varieties of psychotherapy, respectively. An incidental benefit of reading the book is the author's succinct and knowledgeable summaries of the essential features of these various psychotherapeutic approaches. The deleterious consequences of the imposition of values by therapists are emphasized and are portrayed in a thoughtful manner reflecting the ambiguity existing in this area. Certainly it is not easy to differentiate between maneuvers that are ethically legitimate and therapeutically useful and those which are exploitative and self-serving. This dilemma is particularly well illustrated in organizational psychotherapeutic interventions, where the intervenors always have to deal with the stigma of being potential double agents, and also in the tricky ethicalities attached to so-called paradoxical psychotherapeutic interventions. The chapter on marital and family therapies, in which the author describes the ethical demands on family therapists as "the most extreme of any type of psychological treatment," is particularly interesting and somewhat sobering.

The concept of informed consent, which is of recent origin, at least in psychotherapeutic relationships, is prominent throughout the book. Clearly, today's therapist is in a difficult position as he or she navigates between the danger posed by the necessity for legal accountability and the possibly treatment-hampering effects of telling the potential patient too much about what he or she intends to do.

The author closes with a chapter on professional responses to the challenges mounted by the obligation to be ethical in psychotherapy. He stresses the responsibility to be both morally and legally accountable, the need for supervisory training in ethical issues during residency periods and for continuing education afterward, and the potentially prophylactic effect of personal therapy for anyone undertaking a career in psychotherapy. This chapter is a bit thin, and the book could have been made more complete by some discussion of the principles and moral philosophies that must underlie any approach to ethical decision making.

It is worth noting that most of the patients described in this book would be considered as having "difficulties in living" rather than the more severe psychiatric entities.

These strictures aside, I found the book a serious, relatively comprehensive, undogmatic, informed, and interesting discussion of the very pertinent area that it addresses. I recommend *Ethical Issues in the Psychotherapies* to practitioners in the many precincts of psychotherapy.

PAUL CHODOFF, M.D.
Washington, D.C.

FORENSIC ISSUES

Psychological Evaluations for the Courts: A Handbook for Mental Health Professionals and Lawyers, by Gary G. Melton, John Petrila, Norman G. Poythress, and Christopher Slobogin. New York, Guilford Press, 1987, 505 pp., \$50.00.

What kind of questions might lawyers or judges properly put to mental health professionals? Few, some say; for legal purposes, lay persons are quite able to provide evidence concerning mental disorder, and the trier of fact—judge or jury—can reach a decision without the aid of an expert because these cases involve primarily moral and social issues.

Forensic psychiatrists are famous in some circles, infamous in others. To be sure, in many instances their wisdom has been overvalued. The bounds of special knowledge are often exceeded, but, to be fair, it is because questions of all types are thrust upon them. In custody cases involving the issue of visitation, judges ask clinicians to evaluate a child to assess the relative impact of spending 1 week a year versus 2 weeks a year with the father. In cases of sterilization of mentally retarded persons, judges inquire whether scientific breakthroughs will not likely occur that will ameliorate the individual's disability. Lawyers ask for an assessment of an accused person's ability to consult with them (the lawyers) and to understand the proceedings. They ask whether the accused is competent to confess or to plead guilty.

Ask a foolish question, get a foolish answer. These are, of course, just some illustrations of questions put to mental health professionals. In responding, immodesty is not at all apparent. But, surely, it would be surprising and disappointing if those whose study is human behavior could offer nothing useful. Mental health professionals can indeed assist the fact finder in making legal judgments—provided that the professionals know and acknowledge the limits of their expertise, including, when relevant, the lack of a hard scientific database.

The purpose of this book is to provide mental health professionals who are involved in performing psychological evaluations for the courts and lawyers and judges who request such evaluations with a comprehensive guide to the issues the legal system has most commonly asked clinicians to address. The contexts examined in the book are quite diverse: insanity and competency determinations, sentencing and civil commitment proceedings, probate and guardianship hearings, personal injury, workers' compensation and Social Security claims, juvenile delinquency and status offense adjudications, and custody and neglect disputes.

Two of the four authors of the book are lawyers with specialized educational backgrounds in mental health law; the other two are doctorate-level psychologists. One is a university professor with a special interest in children; the other is a practicing clinician who has conducted several studies of the forensic process. Each has trained both mental health professionals and legal practitioners in mental health law. Each has observed or performed scores of psychological evaluations for the courts.

Their collective experience has produced an excellent book, for which they have already received many accolades, including APA's Manfred Guttmacher Award. Each chapter opens with a summary of the relevant legal rules and their underpinnings in jurisprudence, followed by a critical analysis of the law's approach. The authors incorporate or refer to research on each topic. They include studies concerning the reliability of clinical opinions and specific evaluation techniques, actuarial data on those subject to evaluation, and empirical assessments of the manner in which the legal process actually works. For the benefit of both the clinician and the lawyer, they offer suggestions about evaluation procedures and ways of communicating information to the courts. They also provide sample reports. As the subtitle indicates, the book is a handbook that is to be consulted as the need arises. It is a big book, set in rather small type, in two columns.

The adage about too many cooks spoiling the broth does not apply to this work. In this collaborative effort there is little or no repetition or inconsistency. One notable exception, however, is in the discussion of the *Tarasoff* duty to warn or protect. In one place (p. 47) the authors point out

the common misinterpretation given to the case, but in another place (p. 278) they make that very interpretation.

The book might prompt reconsideration by those who debunk the role of mental health professionals in the legal process.

RALPH SLOVENKO, LL.B., PH.D.
Detroit, Mich.

Psychotherapy and the Law, edited by Louis Everstine and Diana Sullivan Everstine. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1986, 277 pp., \$34.50.

Recently no book's title has excited my interest more, and, in the last 10 years, no book has been a greater disappointment. Unfortunately, the book is wrongly named. It is not about psychotherapy and the law but, rather, seems to be an attempt at dealing with the multiple areas of interface of various legal arenas and neuroscience, psychiatry and psychology, diagnosis, and evaluation. Had the editors followed their title, they might have produced a book of great value on a specific topic that has been somewhat neglected. However, they must have confused psychotherapy, a specific entity of different talk therapies, with the greater whole of the academic and clinical fields of psychiatry, psychology, and forensic sciences.

I was particularly disappointed by Louis Everstine's introduction. It seems overly folksy and chatty. For example, he ascribes to Freud opinions that he says Freud would hold today were he alive. The state of psychotherapy, including psychodynamic therapy and psychoanalysis, is so radically different today that it is hard to believe anyone could seriously think they could predict the opinions of such an independent and creative thinker as Freud. But Everstine is quite definitive in many of his statements, often without sufficient referencing.

He raises the "internal debate" over who the client is in psychotherapy. There is no such debate for a medical student, much less a physician. For us there is one patient in the doctor-patient relationship. Is Everstine telling the reader that psychologists have mixed loyalty and less of a commitment in the psychologist-client relationship?

I found his discussion of insanity opinionated, garbled, and confusing. He seems to confuse insanity with psychosis. Further, he begins by blaming psychiatry and federal and state laws for the actions of specific juries in specific cases. No doubt, our legal system is not perfect or foolproof, but many of us who have looked around the world feel we have one of the better systems and that the system is constantly and progressively changing, trying to improve. Louis Everstine proceeds to what seems to me to be a kind of back yard Sunday afternoon philosophizing by blaming mankind as a species for the legal failings.

In his section on dangerousness in the introduction, I found Everstine's assertions to be somewhat clinically naive and his concepts simplistic and unrealistic. He seems to be saying that all patients who are psychotic, whether they are dangerous or not, should be hospitalized. I was surprised by this because I know many instances where nondangerous psychotic patients have been successfully treated as outpatients. Further, I disagree with the statement that nonpsychotic patients are not treated in the hospital. Some certainly are, especially if dangerousness is a component of their psychiatric illness.

Despite the misnaming of the book, some of the chapters

are intrinsically interesting. Prof. Ralph Slovenko gives a clear, cogent, tightly reasoned, and exhaustively researched chapter on competency to stand trial, a topic little related to whether the individual is receiving psychotherapy. The chapter is excellent, well written, and well worth reading for its valuable insights and guidance.

Likewise, Profs. Robert Weisberg and Michael Wald have written a timely and truly thought-provoking chapter on children and confidentiality laws, especially as they pertain to abuse and neglect. They attempt no simplistic formulation but, rather, present the material and the complexity of the issues in a careful, thoughtful, and thorough manner. In addition, they touch on many issues relevant to the practice of psychotherapy, both for adults and children. As both a child and forensic psychiatrist, I found this chapter quite informative and useful.

In my opinion, the positive attributes of this collection of chapters do not overcome the deficits. I was disappointed.

STEPHEN BATES BILLICK, M.D.
New York, N.Y.

Clinical Psychiatry and the Law, by Robert I. Simon, M.D.
Washington, D.C., American Psychiatric Press, 1987, 507 pp., \$29.95.

Ignorance of the law is a stumbling block to providing good clinical care. Dr. Simon does psychiatry a great service by plunging into the formidable task of describing and explaining the areas in which clinical practice and legal regulations overlap. These areas of overlap can cause confusion and discomfort for both medicine and the law. The growing number of laws, regulations, and administrative requirements often serve to increase the distance between doctor and patient and to erode the quality of care provided. For example, in our study in Rochester, N.Y., complicated, time-consuming, and expensive right to refuse treatment court hearings have significantly increased the length of stay and delayed or averted needed treatment (our unpublished data). In order to provide good clinical care in the current environment, a psychiatrist must not only be versed in psychiatric diagnosis and treatment but also have a working knowledge of the pertinent legal issues. As Ralph Slovenko points out in his introduction to this book, "Protecting against liability in the everyday practice of psychiatry has become more difficult than ever before" (p. xxx). We live in a litigious society. Malpractice cases are decided on the basis of adherence or lack of adherence to a professionally developed standard of care. Lacking a standard established by the profession, the court may judicially create a standard of care or invoke the doctrine of strict liability.

This book, which is divided into 24 chapters, may be approached as a textbook to be read cover to cover, as a reference book to answer a specific question in a particular problem area, or as a journal with individual chapters to initiate or supplement one's reading on a particular topic. The reader may find in some of the later chapters that the author expects him or her to have some knowledge of and sophistication in the subject. The reader who is a novice in the area of psychiatry and the law should not be put off by this. Looking to the index or the table of contents will direct him or her to the relevant material to be found in other chapters. For example, chapter 17, "Preventing the Premature Release of Dangerous Patients," refers to the *Tarasoff* obligation to warn an identified victim and includes a dis-

cussion of how *Tarasoff* differs from cases that involve the discharge of an inpatient. (The discharge of an inpatient may involve a duty to the community at large rather than to an individual.) The reader not familiar with the development of the *Tarasoff* doctrine and the issues surrounding it can turn to chapter 16, "Clinical Approaches to the Duty to Warn and Protect Endangered Third Parties," and read the relevant section.

Each of the 24 chapters begins with a clinical vignette that sets the stage for the discussion which follows. The discussion is organized as a response to specific questions. The vignettes, which read like short stories, demonstrate that Robert Simon is not only a knowledgeable forensic psychiatrist but also a skilled, experienced clinician. The use of case examples emphasizes the importance of anchoring theoretical discussions to clinical realities. The first chapter, "Creation of the Psychiatrist-Patient Relationship," begins with a vignette of a young man who was seen by a psychiatrist for a pre-employment psychiatric evaluation. The first question discussed following the vignette is, How is the psychiatrist-patient relationship created? The next question is, What is the legal basis for the psychiatrist-patient relationship? Next follows the question, Must psychiatrists accept all patients who seek their help? The second chapter explores the doctor-patient relationship further and discusses avoiding the role of the double agent. Chapters 3 through 7 focus on psychopharmacological treatment, including the complication of tardive dyskinesia, the right to refuse treatment, and informed consent.

Chapters 8, 9, and 10 deal with issues of confidentiality in clinical practice, the clinical record, and civil commitment. The chapter on civil commitment begins with an especially intriguing vignette and a review of the current trends in involuntary civil commitment statutes, the legal principles forming the basis for commitment laws, and the tension between the legal liabilities imposed on psychiatrists when civilly committing patients and the psychiatrist's traditional clinical role. Chapters 11 through 14 focus on difficulties in the areas of psychotherapy, ECT, seclusion and restraint, and the treatment of suicidal patients. Chapter 15 discusses the sexual misconduct of psychotherapists.

Chapters 16 and 17, as noted, speak to the issues of the diagnosis and treatment of violent or potentially violent individuals with all the hazards of predicting future events. The *Tarasoff* case and its progeny have forced us to struggle with the clinical and statistical reality that psychiatrists are unable to predict rare and distant events with the kind of certainty that courts rely on in arriving at decisions. On the basis of a clinical evaluation, psychiatrists are able to identify seriously mentally ill individuals who, because of their illness, are at some risk for endangering others, themselves, or property in the near future. These individuals may be involuntarily hospitalized for the purpose of evaluation and treatment. The last chapters in the book deal with such interesting topics as innovative therapies, defamation in clinical practice, outrageous behavior on the part of psychiatrists, and the impaired psychiatrist.

A psychiatrist may be an informed, mature, caring clinician who provides excellent patient care and still be sued. Dr. Simon's last chapter deals with malpractice litigation. For there to be a finding of malpractice, the four Ds must be present: Direct Damage to the patient that is the result of a Dereliction of Duty. Simon writes that increasing malpractice premiums can be taken as one measure of the increasing litigation. As P.F. Slawson (unpublished 1988 paper) has pointed out, the claim frequency against psychiatrists con-

tinues to be low when compared with other medical specialties; however, the claim frequency, if not dramatically increasing, is clearly on the rise.

An epilogue by Jonas R. Rapoport, M.D., is followed by two appendices. Appendix 1 is "The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry," and Appendix 2 provides a number of sample forms ranging from authorization of release of medical information to a durable power of attorney for health care.

Clinical Psychiatry and the Law deserves a space on every psychiatrist's bookshelf. Timely, readable, and informative, this book can be pored over many times to the profit of the reader.

J. RICHARD CICCONE, M.D.
Rochester, N.Y.

WOMEN'S ISSUES

The Premenstrual Syndromes, edited by Leslie Hartley Gise, M.D. New York, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1987, 149 pp., \$39.99.

The topic of this book is arguably the most controversial syndrome in psychiatry. It is listed tentatively in Appendix A to *DSM-III-R* under the newly coined term "late luteal phase dysphoric disorder." Dr. Gise wisely retreats from this term, which had promptly acquired the acronym LLDD, and returns instead to the familiar "premenstrual syndromes," implying, in its plural form, a diverse phenomenology for premenstrual changes.

This book consists of 12 updated papers originally prepared for a symposium on the premenstrual syndrome (PMS) at Mount Sinai School of Medicine in New York by gynecologists, psychiatrists, basic scientists, and others.

One of the most welcome changes in psychiatry and in medicine overall has been the organization of patients and their families. PMS Action is one such group. It represents and supports women who suffer from PMS and offers information to professionals who treat women. Its founder, Virginia Cassara, gives a lively account of the most common prejudices and myths about menstruation and premenstrual changes that portray women as vulnerable and unpredictable. I think that Cassara's use of the term "consumer" instead of "patient" is unfortunate because "consumer" literally means "a person or thing that consumes . . . who buys goods or services for personal needs," whereas the traditional term "patient" refers to "a person receiving care or treatment, esp. from a doctor" (*Webster's New World Dictionary*, 3rd college ed.).

PMS Action requires that physicians on their referral list provide progesterone as a treatment option to women with PMS. Undoubtedly, progesterone has been helpful to many women with PMS, but its curative effects have been difficult to prove in controlled studies. Mason gives a careful review of the biological efficacy and pharmacology of progesterone and shows that the deficit hypothesis has not been confirmed by studies examining progesterone blood levels, changes in protein binding, or receptor sensitivity. Interestingly, brain tissues concentrate progesterone: progesterone levels in the brain have been found to be two to five times higher than arterial blood levels. Also, some metabolites of progesterone, which itself has anesthetic properties, have more potent sleep-inducing effects than barbiturates. Mason emphasizes

that progestational agents, especially synthetic progestins, are by no means innocuous substances. They have been shown to have teratogenic action during the early phases of conception, and the large doses (300 mg) of micronized progesterone in oil, much recommended nowadays, can cause dizziness and migraine headaches.

In a well-arranged overview chapter, Chuong and Coulam discuss their area of interest, the endorphin withdrawal hypothesis. Indeed, their investigations have noted lowered plasma endorphin levels during the luteal phase and amelioration of some PMS symptoms following naltrexone administration.

It should not surprise us that descriptions of clinical problems make up the largest portion of this book. Two chapters, one by Endicott and Halbreich on practical problems in evaluation and one by Hamilton and Alagna on the difficulties of conducting human-based research, are a pleasure to read. They are full of tidbits of practical advice on how to think in an enlightened way about converting premenstrual complaints into valid data for research and about how these symptoms fit into a woman's life. Hamilton and Alagna remind us that many of the data used in psychological research are records of alterations in self-perception, which we tend to reify—in a depression or performance score, for instance. These two papers ought to be read before looking at the chapters describing the symptom assessment and treatment of different programs.

There is overlap between chapters, but it proves to be informative, since different PMS clinics emphasize different issues for evaluating and treating patients. Recommendations for what to include in the medical workup and the use of menstrual distress questionnaires are fairly uniform, but the agreement dissipates when it comes to examining psychological functioning. Most programs use a potpourri of traditional personality and mood scales given to patients, from the MMPI to the Eysenck Personality Questionnaire.

Regarding treatment, each of the chapters contains detailed information regarding education, building an alliance for cooperation, dietary guidelines, hormonal treatments, and psychotherapies. Interestingly, PMS has been found unusually responsive to any sort of intervention; in other words, PMS shows a marked placebo effect. The reason for this strong placebo effect is not known. Perhaps the therapeutic contact plus information gives women a greater sense of control and thereby reduces stress, which has been observed to be a major contributor to PMS.

Bruce McEwen, a pioneer in identifying the properties and location of steroid receptors (especially cortisone) in the brain, gives a brief review of the mechanisms involved in the CNS cellular and molecular action of estrogens and progestins. He points out that sexual hormones may have different neurological and psychological effects in men than in women.

Finally, Elizabeth Holtzman, District Attorney in King's County, Brooklyn, provides an animated and well-reasoned chapter on the issues involved in using PMS as a legitimate defense, especially involving the claim of insanity in criminal cases. She argues, I believe persuasively and correctly, that there is no evidence to invoke PMS as a valid legal defense for criminal behavior.

Overall, the syndrome that emerges from these chapters is far from well defined. Despite its distinction in having instantly come under scrutiny from researchers, most of the research still lies ahead. Nevertheless, this stimulating, intelligent, and scientifically up-to-date monograph can be highly recommended to physicians and other professionals. For

those who find the idea of following the fate of a new syndrome in medicine intriguing, this collection narrates the prologue of the story to come.

REGINA C. CASPER, M.D.
Chicago, Ill.

Women in Therapy: Devaluation, Anger, Aggression, Depression, Self-Sacrifice, Mothering, Mother Blaming, Self Betrayal, Sex-Role Stereotypes, Dependency, and Work and Success Inhibitions, by Harriet Goldhor Lerner, Ph.D. Northvale, N.J., Jason Aronson, 1988, 285 pp., \$27.50.

The current women's movement, or the second wave of feminism, a term Dr. Lerner prefers, has brought us immensely valuable insights and shocking discoveries. One would have hoped that clinicians in the mental health field would have made the discoveries on the ubiquity and frequency of rape, incest, and domestic violence and their impact on woman's psychological functioning, but that is not the case. However, some clinicians were quick to recognize the validity and importance of the contributions of feminist thinkers. Dr. Lerner is an acknowledged and respected member of that group. Her contributions to feminist psychoanalysis began during her postdoctoral fellowship at the Menninger Clinic in 1972 and have continued throughout her professional career. This book is a compilation of some of those contributions and as such documents the more important correctives in understanding women's development and functioning that feminism has made.

The list of subjects, teasers you might say, in the subtitle is of great relevance to anyone who treats women or for any reason wishes to better understand the feminine experience. These are topics that Dr. Lerner has addressed repeatedly over the years with unusual balance, thoughtfulness, and clarity. Her lucidity is well complemented by a publisher willing to use clean pages and large clear print, a treat for middle-aged eyes. The book should be equally exciting to young eyes, as Dr. Lerner struggles over and over again to make sense of the consequences of women's subordinate position in society and its effect on family life, professional life, and self-development. Not only is she straightforward and clear, but there is no jargon, no arcane concepts, and none of those unhappy phrases found in early psychoanalytic writing ("psychoanalysis has clearly shown that . . .," for example). Her observations are always clinically derived, explicit, and therapeutically relevant. Her stance is firm, but it invites questions and further investigation. When I found myself in disagreement, I was nevertheless stimulated to rethink my position and I gained from the effort.

Dr. Lerner's ability to deepen our insight by thoughtful exploration of clinical observation is wonderfully presented in "Parental Mislabeling of Female Genitals." This now classic paper, first published in 1976, calls attention to the frequency with which even sophisticated parents name the girl's vagina but ignore her clitoris and vulva as if these sensitive parts of the child's anatomy were insignificant, not a valued part of "what girls have." This may convey a message that the girl should not notice or enjoy this part of her body and may compromise her capacity for pleasure in later sexual life. Dr. Lerner suggests that parents—and society—are apprehensive about girls having sexually sensitive areas and a full sexual life. A sense of castration and penis envy, she suggests, might stem not from anatomy but from the lack

of parental validation of what the little girl's anatomy really is.

In "Adaptive and Pathogenic Aspects of Sex-Role Stereotypes," Dr. Lerner displays the kind of thoughtful and balanced perspective so valuable in her work. She points out that in families in which both parents have a secure and comfortable sense of autonomy and self-worth and a non-conflicted gender identity, a child may benefit from observing nontraditional sharing of tasks and incorporate a definition of his or her gender that sanctions a wide range of feelings and behaviors. However, in a family where self-other boundaries between parents are poorly maintained and one or the other parent has an unstable gender identity, sex-role stereotypes may be clarifying and consolidating to the child and simplify parenting.

In "Female Dependency," Dr. Lerner is concerned that the therapist may see a woman's dependent self-experience and behavior as weak, childlike, and excessive and fail to understand both the social acceptance of this behavior and the patient's conviction that such behavior is necessary to maintain important personal relationships. The therapist may increase the patient's guilt and negative self-image or press for a more assertive, self-confident position without first analyzing the adaptive function being served.

Throughout the book, first as a leitmotif and eventually as the major theme, Dr. Lerner stresses the inadequacy of psychoanalytic or feminist theories that try to understand development from the perspective of the mother-baby dyad alone. First she emphasizes the lack of attention to the father's contribution as if the mother were the baby's environment. She makes us aware that in the triangular relationship of mother-baby-father, each shapes and is shaped by the other. But the triangle is too narrow a focus. Feminists have emphasized the cultural pressures, the subordinate position of women in patriarchal society, and the inhibition of aggression, anger, ambition, and autonomy that society exercises over women's development. These inhibitions play their part in the rates of hysterical personality and depression in women. But Dr. Lerner believes an understanding of these issues requires not only acknowledging the impact of patriarchal culture but also the impact of the multigenerational pattern that personally affects each patient individually and in her current family system. She warns against narrow mother-focused causality in our theories at the risk of ignoring both circular causality within families and interlocking family process. She is concerned with polarized generalizations about gender that create new rigid stereotypes.

Her final chapter, "A Critique of the Feminist Psychoanalytic Contribution," makes a stirring plea to examine female development and self-differentiation from a systemic framework. She deplores current feminist theory that locates the mother-child dyad in the cultural system but leaps over systemic analysis of nuclear and multigenerational family processes. Fathers (and men) have been rendered "to the position of the peripheral other in the domestic sphere, just as women have been so rendered in the public domain" (p. 270). Only by examining and questioning the interacting elements in the immediate family and in the family of origin can women (and men) increase their self-differentiation and develop a more adaptive and flexible balance in their emotional lives. This active reconstructive process is especially important for women because their historical context has been submerged by the history of male society. By reestablishing a continuity of feminine experience her past becomes relevant to her identity and enhances differentiation in the present.

This review cannot do justice to the impact of Dr. Lerner's final chapter. All the other chapters have appeared previously, mostly as papers. This chapter is totally new and thus will be read only by those who buy the book. I hope many will because it has great strengths, beauty, and persuasive power. But I am worried by a statement Robert Stoller made to me some years ago. In response to my request for a book chapter from him, he said, "If you want your ideas to be read, don't put them in chapters for books; publish a paper." I trust the prophecy will not affect this provocative work. It deserves a wide audience and should be read by everyone hoping to further their understanding of women.

MARTHA KIRKPATRICK, M.D.
Los Angeles, Calif.

Untold Lives: The First Generation of American Women Psychologists, by Elizabeth Scarborough and Laurel Furumoto. New York, Columbia University Press, 1987, 226 pp., \$27.50.

As scholars seek to restore women to their appropriate place in history, each discipline has examined its roots and origins. Each has discovered the extraordinary contributions of the women who pioneered but were often neglected or relegated to footnotes in the history of that discipline. In *Untold Lives*, the authors examine the lives and contributions of nineteenth-century female psychologists. They have dedicated themselves to debunk the "myth of a womanless history" (p. 1).

During the last century the separateness of men's and women's spheres of interest and activity was widely accepted. Although women were expected to conform to specific female roles, these expected roles and the actual behaviors of women were not necessarily congruent. Women increasingly moved into the labor force, higher education, and politics. Women began to enter the professions and, despite vehement protests and some preposterous views regarding their deficiencies, persevered and succeeded.

During its formative years in the latter part of the nineteenth century, a number of women were active participants in the field of psychology. From the beginning, the membership of the American Psychological Association included women. At its 25th anniversary, in 1917, women represented 13% of the membership. Despite these figures, however, the authors note that the contributions of women in psychology remained largely ignored.

Untold Lives begins by focusing on the women who are identified as psychologists in the 1906 edition of Cattell's *American Men of Science*, the first comprehensive directory of scientists in the United States. Those included were self-identified and met minimal specifications; of the 4,000 individuals included, 200 were psychologists and 19 of these were women. In addition, the authors included those women who were members of the American Psychological Association by 1906. They chose 25 women to represent the first generation of women psychologists.

The authors look at these women in terms of their contributions to the history and development of psychology. Their experiences are reconstructed, and the differences between them and the early male psychologists are examined. In each chapter, the authors provide an illustration of a particular gender-specific theme. Underlying, however, are the basic concerns experienced by women in all fields: denial of op-

portunity and the conflict between nurturance and achievement. Each history in the book is captivating, concise, and focused.

In the second section of the book a collective portrait of the careers and contributions of these 25 women takes us to the present to look at the shifts in focus of the field and the paths of women psychologists, who continue to see themselves as part of the mainstream yet often quite separate. The number of woman psychologists in the United States has continued to increase, and their influence has also expanded. They have been leaders in research, clinical work, and organizational involvement. The authors caution, however, that "devaluation of whatever is produced by women continues as a widespread though often unacknowledged attitude. There is little reason to believe that historians are exempted from this cultural handicap."

This volume documents an important component of the history of a profession. It has important implications for all professions.

CAROL C. NADELSON, M.D.
Boston, Mass.

Sexual Contradictions: Psychology, Psychotherapy, and Feminism, by Janet Sayers. London, Tavistock, and New York, Methuen, 1986, 203 pp., \$29.95; \$12.95 (paper).

This book is about man's social dominance and women's resistance to it. Three categories of theories are currently invoked to explain women's status. These are biological, cognitive-developmental, and social. Only Freudian theory accounts for women's resistance to domination by men.

Review of the evidence for biological determinism reveals equivocal results. Consistent correlation between hormonal levels and traits that are considered masculine (aggressiveness and initiative, for example) is lacking. The theory that sex differences are learned in the course of development is challenged by the rebellion against the acceptance of stereotypical roles and behaviors. Some theories focus on societal rewards and punishments as motivation for adherence to gender roles, but this fails to account for similarities in behavior in societies in which different social norms are stressed.

Following Freud, theories to elucidate sex differences were promulgated that either denied, modified, or elaborated some aspects of Freudian theory. Horney argued that men fear, envy, and are in awe of the innate, biologically determined child-bearing and nurturing capacities of women, but that women's envy of the penis and their innate submissiveness account for women's acceptance of a position of inferiority. Proponents of feminism like Rich and Irigaray claim that denial of their sexuality is an important factor in women's acceptance of inferiority.

Melanie Klein emphasized that the love and hate (based on instinctual forces) engendered during the early experiences with the mother as giving or depriving profoundly affect development. The male's rebellion against his all-powerful mother motivates his desire to dominate women, but, as Sayers points out, does not account for the woman's submissiveness or her rebellion.

For the object relations theorists (Fairbairn, Winnicott, and Kohut, for example), the actual relationship with the mother is pivotal. Separation from the mother and the establishment of autonomy are crucial issues in which the nature of the early ties to the mother is reflected. The closeness

between mother and daughter, based on identification with each other, results in an experience of intimacy that boys do not have. Because of these different experiences, concern for others is associated with caretaking and nurturing qualities in females and self-sufficiency and individuality are more important to males.

Lacan objects to the attribution of gender identity to preoedipal issues; he does not believe that there is an innate sense of gender. A concept of gender, he believes, is not possible before anatomical differences can be appreciated. Thus, the castration complex is an essential component of the awareness of gender. The phallus, according to Lacan, symbolizes "the law of the father." The absence of the phallus accounts for women's inferiority. Patriarchal society reinforces these ideas.

Sayers believes that most theories of femininity fail to consider the contradictions inherent in female psychology. Women wish that both their similarities to and their differences from men would be considered. Freud was aware of these contradictory desires as he was aware of the ubiquity of psychological conflict. Males and females seek both active and passive gratification. Anatomy and social pressure are determinants of the possibility of gratification. Although anatomy clearly defines certain behaviors, there is a wide range of behaviors that have been considered sex-linked but are not.

It is well-known that Freud attributed much maladaptive behavior to the repression of sexuality. He delineated the intricate processes involved in this phenomenon. Sayers' statement that Freud believed that repression was motivated by societal disapproval is inaccurate. Although Freud recognized the role of society in the production of neurosis, he stressed the importance of conflicts within the individual as a source of psychic distress.

Sayers discusses projection, depression, and paranoia as ways to elude the consciousness involved in social experience (p. 136). As in her discussion of repression, she addresses cogent issues but her presentation is flawed by her failure to give sufficient weight to intrapsychic conflict; she addresses only the conflict with society.

Sayers is rightfully critical of those who conceptualize female psychology in unidimensional terms. She endorses Freud's view that psychic conflict is a central feature of human activity and that awareness of it is essential for effective functioning. Resolution of conflicts regarding femininity is a prerequisite for the implementation of the means to improve the situation of women. To accomplish this, conflicts within the individual as well as those between the individual and society need to be addressed. The book is limited because of Sayers' neglect of the intrapsychic.

REBECCA Z. SOLOMON, M.D.
Hartford, Conn.

SOCIAL AND ECONOMIC ISSUES

Mental Health and the Environment, edited by Hugh L. Freeman, M.Sc., M.A., B.M., B.Ch., F.R.C.Psych., D.P.M. New York, Churchill Livingstone, 1984, 469 pp., \$69.00.

The pages of this heavyweight edited volume are dense with quotes and references to studies in such diverse areas as geography, child welfare, ethnology, architecture, urban planning, sociology, education, anthropology, ecology, gen-

eral and occupational medicine, and, of course, psychology and psychiatry. There is nothing dramatic either in the presentation of copious data or in the conclusions that are reached. In fact, the book offers an indispensable, albeit sometimes ponderous, foundation for those who are interested in developing a psychiatry of the environment.

Hugh Freeman, the book's editor, is one of England's psychiatric luminaries, and his long-term clinical work with urban working-class populations is evident in his insightful introduction and in his chapter, "The Scientific Background." His ability to organize and to synthesize an incredible amount of material is an editorial tour de force. Among the topics covered are social networks, stress, personal space, crowding and density, stimulus overload, noise, urban malaise, the environment and children and the elderly, the environment and depression, social processes (disintegration, rigidity, isolation, stress, class, drift, and residue), and ecology.

As Freeman notes, the concept of environment is so broad as to include all the outside influences experienced by an organism's genotype from the moment of conception up to death. He neatly narrows matters by considering "those characteristics of peoples' physical and social surroundings for which there are reasonable grounds to suggest that they are likely to be significant in relation to mental health and illness" (p. 2).

The only disappointment I had was a realization that nothing grand or universal can be deduced from the many studies cited in the book. Indeed, the opening chapter begins, "To start on a note of caution, it is very unlikely that direct cause-and-effect relationships will be found between specific features of the environment and abnormal mental states or forms of psychological malfunctioning" (p. 23). The following quotes typify much of the book's contents: "Environmental factors seldom appear to have immutably positive or negative influences on aggression, so that each individual example of apparent behavioural disturbance must be considered on its merits" (p. 115). "Although attempts have been made to relate general psychiatric/sociological explanations to the individual case and to explain how it comes about that certain children and adults in certain environments do in fact come to behave in an anti-social manner, none of them has been formulated in terms susceptible of empirical verification" (p. 191). "Noise occasionally appears to affect health directly, but generally it operates through the mediation of psychological and constitutional factors of which little is known" (p. 267).

In conclusion, this important reference work summarizes what is known about a vast area of social psychiatric concern, namely, the relationships between behavior and the environment created by architects and planners. However, a melancholy tone pervades the book because of the recurrent observation that economic considerations almost always have taken precedence over concerns about the human consequences of urban planning, architectural style, industrial patterns, and transport development.

ARMANDO R. FAVAZZA, M.D., M.P.H.
Columbia, Mo.

Handbook of Quality Assurance in Mental Health, edited by George Stricker and Alex R. Rodriguez. New York, Plenum, 1988, 509 pp., \$50.00.

Quality of care is like happiness: everyone wants it, but no one can articulate exactly what it is that they want. When

confronted with cost-containment efforts, a major rallying cry for the profession is that the quality of care is being compromised. Quality of care measures such as utilization review and case management have increasingly been used in the effort to regulate the cost of psychiatric care. This has led to a growing need to understand precisely what we mean by quality in the field of psychiatry and in the treatment of mental illness. Quality "assurance" implies the accounting aspects of care—that is, costs which are associated with the delivery of definable services, most often paid by fiscal third parties.

The *Handbook of Quality Assurance in Mental Health* has a lot to say on the subject of quality assurance. Psychiatry is broad, and when broadened to include "mental health" this book on quality of care is potentially expanded to an exegesis on quality of life. This could include the quality of many variations of psychotherapy for all kinds of problems (in addition to identifiable *DSM-III-R* psychiatric conditions) and also could apply to the evaluation not only of physicians and psychiatrists as therapists but also psychologists and social workers. This book, however, sticks mostly to the basics of quality assurance.

A wealth of experience in quality assurance has accumulated in the last 20 years in many different settings, and this book is the most complete compilation of that experience from a variety of perspectives: providers, settings, and consumers. It is organized in five parts. The lengthy introduction by Dr. Rodriguez brings into focus all of the issues of the succeeding chapters, including the uncomfortable tradeoffs for patients who need costly long-term care, the emerging power of payers in determining professional practice, and the adversarial nature in some of the interactions between reviewers, providers, and patients. Dr. Rodriguez is prolific on the subject.

Part two, General Issues, is a potpourri of historical trends, research and evaluation, education, economic conditions, the role of the consumer, and alternative futures. Part three, Level of Care, focuses on acute inpatient services, outpatient therapy, and the influence of external forces on the quality assurance process. Indeed, it is this bellwether issue which pervades the entire book; that is, the other parties (insurance companies, large employers, government) who are most concerned about costs seem to be driving the quality assurance machine. The chapter on the influence of external forces on quality assurance practice by Dr. Robert Gibson is especially valuable.

Part four, Administrative Structures, looks at the roles of the federal government and the state, legal considerations, the roles of professional associations, and quality assurance activities for mental health services and health maintenance organizations (HMOs). In the chapter on HMOs, Dr. Michael Bennett tries very hard to define the ephemeral nature of quality without focusing on the purely mechanistic aspects. On the basis of a survey of HMOs, he came up with the findings summarized in a subsection of his chapter labeled Current State of the Art: Zen and the Art of Quality Assurance.

The final section, Mental Health Programs, reviews current systems of evaluating quality care in a professional association, a hospital, a university counseling center, and an HMO modeled on an individual practice association (IPA).

After carefully perusing this immense volume, I was still left bewildered by the question posed. What is quality? I know that if I get sick I want quality care. More efforts must be made by everyone concerned—patients, providers, and third-party payers—to define what it is we want to achieve

and how much we want to spend. Then we must spend most of our time doing the best job we can to reconcile the difference.

One important aspect of quality assurance not addressed adequately in this book is the cost of the process to the patient and the provider, especially in the cases of severely ill individuals who need extensive inpatient care. More and more time is being diverted to reviews of managed care for these patients, and hospitals find themselves in the position of justifying more extensive active treatment in the face of vague and conflicting rules and multiple reviewers. Ethical issues are surfacing, especially in relation to the treatment-resistant catastrophically ill patient. These patients do not respond to standard short-term interventions and are often noncompliant with the treatment provided. They are young and present a substantial disability burden to the community at large. There is the need for data on length of stay and outcome that will allow a more equitable process for determining the allocation of resources for the treatment of such patients (1).

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STEVEN S. SHARFSTEIN, M.D.
Baltimore, Md.

DISSOCIATION

Split Minds/Split Brains: Historical and Current Perspectives, edited by Jacques M. Quen, M.D. New York, New York University Press (Columbia University Press, distributor), 1986, 177 pp., \$38.00.

This book contains papers presented at a 1984 symposium on historical and current perspectives on dissociation. The usual causes for complaint in collections—uneven scholarship, indifferent writing, redundancy—are not much in evidence here. Its malady is a sort of identity crisis as it searches for its intended audience.

The book aims to promote understanding of multiple personality disorder among psychiatrists, historians, and sundry others. Indeed, many who are interested in hysteria and multiple personality disorder will want to peruse Carlson's fine opening chapter on the history of dissociation. Most readers, however, will find historian Decker's "The Lure of Nonmaterialism in Materialist Europe" heavy going, and another historical think piece, "The Fragmenting of the Soul," embraces a scatter-shot style of punctuation that ultimately obscures the line between comma and coma. And what is the historian (or anyone else) to make of a 22-page chapter that answers in the negative the question, Can neurological disconnection account for psychiatric dissociation?

Saving graces in this book include Adam Crabtree's clear exposition of how dissociation was explained during the early twentieth century and Putnam's equally clear presentation of the historical background of multiple personality disorder, from which we learn, among other things, why we have never found answers to some of the questions (e.g., Is it real?). Lawrence Kolb takes another bite of the posttrau-

matic disorder apple, and, finally, we shudder through a half-in-fun discourse on horror and dissociation, largely a meander through Poe's "The Murders in the Rue Morgue," which probably went over better as a talk than it does on paper.

This is a too-varied collection that strains for cohesion.

Read the good bits in the library. At best, it rates a split decision.

JAMES MORRISON, M.D.
San Diego, Calif.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Dangerously Aggressive Behavior as a Side Effect of Alprazolam

SIR: Recent reports have expressed concern about side effects associated with alprazolam. Juergens and Morse (1) reported agitation, depersonalization, and perceptual distortion in patients during withdrawal from alprazolam, and Noyes et al. (2) noted mania, amnesia, and aggressive behavior. Pyke and Kraus (3) reported intolerable irritability, suicidal depression, and assaultive behavior in patients who had histories of major depression. The purpose of this communication is to confirm and extend the warnings of these investigators by reporting an episode of dangerously aggressive behavior in a patient who had taken alprazolam.

Mr. A, a 34-year-old man, had no history of symptoms indicative of bipolar disorder and no history of aggressive or violent behavior. His occupational history in a management position was good. His medical history was unremarkable except for one episode of head trauma, inflicted by his wife with a baseball bat about 6 months before the episode in question. Although Mr. A had continued to work, his family reported that he was changed and that he had difficulty organizing his thoughts following the incident with the baseball bat. An EEG was interpreted as indicating abnormality consistent with the history of head trauma. His physician had treated his situational depression with amitriptyline, 25 mg h.s., for approximately 1 month and subsequently with alprazolam before the aggressive episode occurred.

In that episode, in the midst of marital discord, Mr. A had taken all of the alprazolam available to him (apparently, about 10 mg). When he awakened after about 8 hours of sleep, he and his wife had begun to argue. He reported that he recalled leaving the house and throwing rocks at the windows of their truck. In an ensuing wild drive, he realized that police officers were shooting at the truck and thought, "They should shoot higher to kill me." After a chase by numerous police officers, during which he drove at high speed directly toward several police cars, the truck left the road, rolled over approximately five times, and burst into flames. He was pulled from the blazing truck by an officer with whom he wrestled.

Five months later, Mr. A presented as a generally normal-looking, appropriately anxious and concerned 34-year-old man, with no substantial abnormalities on interview and on mental status examination, who expressed regret concerning his dangerous behavior. His MMPI results, in marked contrast to his appearance on interview, presented evidence of major depression. Nothing in this man's previous history would have suggested an outburst of potentially lethal behavior. In retrospect, his extremely high MMPI depression scale score ($T=104$, 5.4 standard deviations above the mean) probably reflected in part a situational depression due to his very serious legal situation following the episode. However, his history of depres-

sion and his extremely high depression score are indicative of chronicity.

This case extends the observations of previous investigators in emphasizing that the side effects of a high dose of alprazolam may be hazardous. The importance of major depression as a risk factor has previously been emphasized. It is to be hoped that future case reports will elucidate the relevance of brain damage as another factor predisposing individuals who take high doses of alprazolam to aggressive behavior.

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ALFRED P. FRENCH, M.D.
Sacramento, Calif.

Delirium With Dystonia: A Variant of Neuroleptic Malignant Syndrome?

SIR: We report a 3-hour episode of acute delirium, dystonia, and autonomic changes that improved dramatically after two doses of intramuscular benztropine given one half-hour apart. Even though this case did not meet the usual criteria for neuroleptic malignant syndrome, we think that it could be a variant and that it belongs in a spectrum that includes neuroleptic malignant syndrome.

Mr. A, a 24-year-old man, was admitted to the hospital because of a recent assault, paranoid delusions, and auditory hallucinations. At age 17 he had had the first of several hospitalizations for a paranoid schizophrenic illness, and he had been treated off and on with neuroleptic medication for the 7 years before this latest admission.

On the day of admission, Mr. A was started on a regimen of haloperidol, 5 mg p.o. three times a day. By evening he had received 10 mg, and it was noted that he was confused, was experiencing a feeling of centipedes crawling over his body, and was picking at his skin. He became increasingly agitated and received an additional 2.5-mg dose of haloperidol intramuscularly.

Minutes after the injection, Mr. A began to exhibit total body rigidity, with intervening spasms of the arms and legs and opisthotonos, and began to sweat profusely. His vital signs before the intramuscular injection were temperature, 37.1 °C; blood pressure, 130/70 mm Hg; pulse, 72 bpm; and respiratory rate, 16 breaths/minute. As the episode

progressed, his temperature increased to 37.8 °C, blood pressure to 160/84 mm Hg, pulse to 100 bpm; and respiratory rate to 28 breaths/minute. He became increasingly confused, agitated, and disoriented.

There was no response to an intramuscular injection of 2 mg of benzotropine. A second injection of 2 mg of benzotropine was given a half-hour later, and within 5 minutes his spasms ceased, the rigidity and tachypnea improved, the sweating subsided, and Mr. A relaxed and fell asleep. The next morning the patient showed no signs of delirium or rigidity but continued to be paranoid and delusional.

In reviewing this case, we were impressed that delirium was a prominent feature, whereas it is often listed in the literature as a minor criterion for neuroleptic malignant syndrome (1). The total body rigidity, diaphoresis, autonomic changes, and delirium suggest neuroleptic malignant syndrome, even though the patient's temperature was not extremely elevated. His creatine phosphokinase level was not determined. We feel that in this case, delirium could have been an early sign of an evolving neuroleptic malignant syndrome or a variant. Deuschl et al. (2) may be correct that a dopaminergic-cholinergic balance is altered in neuroleptic malignant syndrome, resulting in a relative hypercholinergic state.

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JERRY J. DOWLING, M.D.
V. PATRICK, M.D.
Kaneohe, Hawaii

Delirium in Runners

SIR: Classical heatstroke is a disorder of the elderly characterized by severe hyperpyrexia (temperature up to 47 °C), dry skin, and respiratory alkalosis (1). The initial presentation during a heat wave can be convulsions, but mental status changes—restlessness, confusion, etc.—are usually the premonitory signs and symptoms.

In the last decade long-distance running has become popular for its alleged mental and emotional benefits (2). Running exertion has made physicians appreciate a new diagnostic entity, heat exhaustion (1). This is a disorder of young, healthy athletes; it is associated with pyrexia (temperature up to 43 °C), sweaty skin, lactic acidosis, rhabdomyolysis, disseminated intravascular coagulation, acute renal failure, hyperuricemia, and hemoconcentration (1, 3). Hypoglycemia and dehydration often complicate it (1, 3). In relationship to heat stroke, heat exhaustion represents a different degree of severity on the continuum of disordered thermoregulation (1). Psychiatric symptoms are also very common in heat exhaustion. For example, of 29 patients diagnosed as suffering from heat exhaustion during the Peachtree Marathon, 10 were confused and three were delirious (4). Although one internal medicine case report (5) has described psychosis as an initial presentation in heat exhaustion, to our knowledge, there have been no reports in the psychiatric

literature of heat exhaustion with resultant delirium induced by long-distance running. We report such a case.

Mr. A, a 30-year-old white man, was found by his friends, wandering around his apartment, agitated and shouting incoherently. He attacked the ambulance driver and had to be restrained by the police, who took him against his will to a psychiatric emergency service, where he was also restrained. His blood pressure was 90/60 mm Hg, his heart rate was regular at 120 bpm, and his respiratory rate was 20 breaths/minute. He failed to cooperate with attempts to take his temperature by mouth. During the initial examination it was noted that he was dressed in a running outfit covered with brush and grass; he was belligerent, disoriented in all three spheres, and unable to give a coherent history, to cooperate with formal parts of the mental status examination, and to maintain his attention on the examiner. The results of a physical examination were within normal limits except for severe sweating.

The initial psychiatric diagnosis was delirium of unknown etiology. Mr. A's friends claimed that he had no previous psychiatric history, he did not abuse drugs, and he had been in a race that morning. Heat exhaustion was then suspected. His rectal temperature was 37.5 °C, and his BUN, sodium level, hematocrit, hemoglobin level, and WBC count were elevated, which is indicative of hemoconcentration. Results of toxicology studies were negative. The patient was treated with ice packs to the neck (1, 3, 4) and 1,000 cc i.v. of normal saline. Within 1 hour he became coherent and gave the following history: he had run 6.3 miles that day—an unusual distance for him—and he did not remember finishing the race or how he got home to his apartment.

Mental impairment in a runner with heat exhaustion is directly related to the rectal temperature (1, 4). Because early warning symptoms of heat exhaustion are difficult for a runner to recognize, we expect that free-standing psychiatric emergency units may encounter this presentation in the future. Because of the potentially serious consequences of this condition (1, 3, 5), early recognition and immediate definitive treatment (cold packs, rehydration, 50% glucose, etc.) are indicated (1). This diagnosis should be considered for any patient presenting with delirium if that patient has recently been running, is pyrexia, and shows hemoconcentration on laboratory examination.

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DAVID A. FISHBAIN, M.Sc., M.D.
MYRON GOLDBERG, PH.D.
Miami Beach, Fla.

A Case of Severe Lithium Toxicity Induced by Combined Fluoxetine and Lithium Carbonate

SIR: Several cases of mania precipitated by the selective serotonin reuptake blocker fluoxetine have been reported (1–3). We report a case in which severe lithium toxicity was induced by the combination of fluoxetine and lithium. The symptoms resolved spontaneously within days when fluoxetine was discontinued.

Ms. A, a 44-year-old woman with a diagnosis of bipolar affective disorder, had been successfully maintained on lithium carbonate therapy for the past 20 years without complications. Her lithium dose was 1,200 mg/day, and her serum lithium levels ranged from 0.75 to 1.15 meq/liter. Results of routine laboratory workups over the years, including kidney function tests, were all within normal limits. Three weeks before her admission to the hospital, she complained of weakness, tiredness, decreased ability to concentrate, and early morning awakening. Her family physician prescribed fluoxetine hydrochloride 20 mg/day, to be added to the lithium. Within a few days Ms. A developed stiffness of her legs and arms, dizziness, and unsteadiness in walking. Her gait became ataxic and her talk dysarthric. On her admission to the hospital, a blood specimen revealed a substantial increase in her serum lithium level to 1.70 meq/liter. The fluoxetine was discontinued and the lithium dose was decreased to 900 mg/day. Ms. A's serum lithium level dropped to 1.20 meq/liter within 48 hours. The disturbing neurological symptoms disappeared within 7 days, and the serum lithium level dropped further to 0.90 meq/liter. An EEG and a brain scan showed no abnormality. Ms. A's condition remained stable at that serum lithium level, without any recurrence of her neurological complications.

While the mechanism of the ataxic symptoms induced by antidepressants is unknown, it is possible that an acute shift in the balance of dopaminergic and cholinergic transmitters in the putamen or caudate nucleus is involved. Added to this, manic patients have an increased vulnerability to lithium neurotoxicity (4). It is also well established that mania can occur during treatment with fluoxetine alone, so the combination with lithium should be discouraged (1–3), and investigators should be aware of the possible complications with the combination.

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AZIZ A. SALAMA, M.D.
MOUSTAFA SHAFEEY, M.D.
Springfield, Ill.

Should Dementia Be Recorded on Axis II?

SIR: One of the important innovations that came with the introduction of *DSM-III* was the multiaxial system of diagnosis. The introduction of a separate axis II dimension has since allowed clinicians and researchers to document personality disorders and developmental disorders separately from the presenting psychiatric syndrome on axis I. Axis II thus provides an orienting frame of reference for more appropriate formulation of treatment plan and prognosis.

I suggest that the planners for *DSM-IV* consider including dementia as another condition to be recorded on axis II. In contrast to disorders currently assigned to axis II, dementia is obviously not an early-onset, lifelong condition. However, similar to mental retardation and personality disorders, dementia typically presents as a "background" condition in psychiatric patients. The patient comes to our attention because of derivative problems, such as secondary psychotic symptoms, mood disorder, delirium, anxiety, or combative behavior. In fact, uncomplicated dementia in itself is not a condition calling for psychiatric expertise. The correction of underlying causes, rarely as they are found, is managed by neurosurgeons, endocrinologists, etc. In the exceptional case where the cognitive impairment itself is indeed the only or the primary target of psychiatric intervention, the qualifier "principal diagnosis" could be used.

Phenomenologically, dementia and mental retardation can be identical. I have found that conceptualization of mental retardation as an axis II disorder is helpful. I believe dementia should be thought of, and therefore coded, in a similar way. One day in the future, when specific treatments for the alleviation or reversal of primary degenerative dementia may become available, the situation would change. In that case, appropriate coding would need to be reconsidered.

OLE J. THIENHAUS, M.D.
Cincinnati, Ohio

Anticoagulant Therapy for Aggressive Dementia Patients

SIR: A letter from Stuart C. Yudofsky, M.D., and Jonathan M. Silver, M.D. (1) mentioned the pathogenesis and treatment of aggression associated with organic brain syndrome, and this reminded me of the experiences my colleagues and I have had with violence in organic syndrome patients (2). Almost without fail the aggressive activity gradually disappeared as the anticoagulant therapy prescribed for improving the blood circulation in the brains of these dementia patients took effect. One woman had been beating her daughter over the head with her high-heeled shoe, another gave her daughter-in-law bruises on the legs with her cane, and a husband had begun shoving his wife around in anger. They were started on small doses of haloperidol for immediate help, but 5–8 weeks after warfarin sodium had been started and an adequate prothrombin time had been attained, there was only occasional need for a tranquilizer. For all of these patients, what had appeared to be a need for imminent institutionalization was avoided. This has happened so often that I now tell the relatives that even if the patient's memory does not improve, we can nearly always relieve the aggressive behavior, and with little or no tranquilizer, so the patient's reactions are not obtunded.

I assume from these experiences that the aggression results from anoxia of the brain cells due to cerebrovascular insufficiency in the part of the brain controlling violent behavior.

The anticoagulant appears to be the beneficial factor, since, ordinarily, the patients would revert to aggressiveness if haloperidol were causing the improvement and the drug were discontinued. The method of action of the anticoagulant is to improve the circulation by reducing the agglutination of the blood cells in the narrowed arterioles, capillaries, and venules, as suggested by Knisely and his co-workers (3, 4).

I have not had the chance to try this therapy regimen on patients with aggressive outbursts who have had head injuries, but I expect they might respond well, since their vessels are likely to be injured and narrowed by the trauma, which would render them susceptible to aggregation of blood cells, causing ischemia of small areas of the brain. This therapy approach should be tried, considering the number of such patients who are having this problem. The risks of some of the medicines being used now rival, or perhaps even exceed, the risk of carefully controlled anticoagulant therapy, which may have the advantage of offering a much better result.

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ARTHUR C. WALSH, M.D.
Pittsburgh, Pa.

Schizophrenia, Panic Attacks, and Antidepressants

SIR: We read with interest the article by Jeffrey P. Kahn, M.D., and associates (1) on the effect of alprazolam in decreasing panic anxiety and in improving some psychotic symptoms in schizophrenic patients. We report two patients who met the *DSM-III-R* criteria for residual schizophrenia and who also had panic attacks. Imipramine, a tricyclic antidepressant, was effective in treating these attacks.

Ms. A was a 35-year-old white woman who had had schizophrenia for about 5 years. Formal thought disorder and delusions characterized the clinical picture at the onset of the illness. The patient had been taking a combination of 4 mg of perphenazine and 25 mg of amitriptyline three times a day for about 9 months. She continued to have symptoms of paranoid ideation, auditory hallucinations, blunted affect, and overinclusive thinking. Within a few days of substituting perphenazine, 4 mg t.i.d., for the combination, Ms. A started experiencing episodes of intense anxiety associated with palpitations, chest discomfort, shakiness, and sweating. She reported that she had had these symptoms for several years before starting to take the combined medication. Thus, these attacks did not appear to be due to withdrawal from the combination. Because of an increase in the frequency and severity of the anxiety attacks, about 18 months after the combination of drugs was stopped, Ms. A was placed on a regimen of imipramine, 25 mg/day, which was subsequently increased to 50 mg/day. She reported moderate to marked improve-

ment in her anxiety attacks. No change was observed in her psychotic symptoms.

Ms. B was a 36-year-old white woman who also had had schizophrenia for about 5 years. At the time of the current evaluation, she presented with looseness of associations, persecutory delusions, and blunted affect. She also complained that she had had episodes of extreme nervousness, palpitations, shakiness, and sweating for several years. She was taking thiothixene, 15 mg/day, benztropine, 2 mg/day, and triazolam, 0.25 mg h.s. A previous increase in her dose of neuroleptics had not resulted in improvement of her anxiety attacks. When Ms. B was placed on a regimen of 25 mg/day of imipramine, which was increased to 50 mg/day, there was a moderate to marked improvement in her anxiety attacks, and she became more comfortable in social situations. She was also able to discontinue the triazolam without any problems. There was no change in her psychotic symptoms.

These reports are in agreement with the findings of Kahn et al. (1) and suggest that schizophrenic patients who have concomitant panic attacks benefit from antipanic drugs in addition to the antipsychotic medication. In our patients, antipsychotic medication did not appear to have an effect on panic anxiety, and low doses of imipramine did not exacerbate psychosis.

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VIKRAM K. YERAGANI, M.D.
RICHARD BALON, M.D.
ROBERT POHL, M.D.
Detroit, Mich.

Patients' Surreptitious Taping of Forensic Psychiatric Examinations

SIR: Lawyers have argued that surveillance of the forensic psychiatric examination is necessary to protect clients' rights and ensure more accurate reporting of the findings. Psychiatrists have expressed concerns that surveillance might introduce contaminating factors which could impair the validity of such examinations. The current state of scientific knowledge about this issue does not allow us to assess confidently whether the perceived need for surveillance safeguards outweighs the possible cost in terms of interfering in important ways with the validity of forensic examinations (1). In this context, I would like to report a new phenomenon, of which all psychiatrists should be aware, that adds a novel and disconcerting dimension to this controversy, namely, surreptitious surveillance of the examination by the *patient*.

Whereas psychiatrists (and lawyers) are prohibited by their code of ethics from surreptitiously taping patients (or clients), neither legal sanctions nor specific ethical restrictions in any way act to bar examinees from surreptitiously recording their own psychiatric sessions (2, 3). The forensic examination evokes substantial elements of secondary gain and adversarial tension. Under these circumstances, the examinee may view electronic eavesdropping as a form of jus-

tified "self-help," on the basis of motives ranging from psychotic concerns to reality-based perceptions of a need for self-protective measures. The following case is illustrative of this phenomenon.

Ms. A, a 32-year-old woman, was charged with conspiracy to sell a controlled substance and obstruction of justice. Her past psychiatric history and present bizarre behavior were the basis for a court-ordered examination to assess her competency to proceed to trial. During the examination, she indicated that she believed that the psychiatrist, the presiding judge, and her own lawyer were plotting against her. She accused the psychiatrist of being a Mafia informer who was determined to have her declared incompetent in order to silence her. During a hearing on the issue of her competence, she attempted to introduce into evidence a tape recording she had made surreptitiously during the examination. She insisted that the tape would prove conclusively that the psychiatrist was conspiring against her. The court refused to admit the tape into evidence. She was found to be incompetent and was remanded for psychiatric treatment.

In this era of sophisticated electronic technology, the examinee who is "wired for sound" may become an increasingly familiar phenomenon in criminal cases, child custody disputes, and other areas of litigation (including psychiatric malpractice).

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ROBERT LLOYD GOLDSTEIN, M.D., J.D.
New York, N.Y.

Psychoanalysis in the Soviet Union

SIR: A recent front page story in the *New York Times* heralded the emergence of interest in psychoanalysis under the new conditions prevailing in the Soviet Union. The correspondent quite correctly said that the USSR had neglected and basically rejected psychoanalysis, but it is interesting to note that Freud, in the past, had some friends in Russia. The first translations of Freud's work appeared after the October Revolution, and for 10 years there was a Leningrad chapter of the International Psychoanalytic Association, under the leadership of Dr. M. Wulf, who later emigrated to Israel. At that time A.R. Lurii, their leading psychologist, was a member of the editorial board of the *International Journal of Psychoanalysis*, as was I.V. Kannabikh, a venerable and respected psychiatrist and historian of Russian psychiatry. In that period an American psychoanalyst, Frankwood E. Williams, wrote enthusiastically of Soviet psychiatry. Eisenstein, the great motion picture director, was much interested in Freud. In the 1930s psychoanalysis was widely criticized and fell into disrepute; psychotherapy in general was played down, although never entirely, for Soviet brands of Pavlov-

ian and reflexological psychotherapy were practiced. In more recent years a Leningrad school of psychotherapy under Miaschechev was active, and an American psychoanalyst, Dr. Ziferstein, worked there for a year with sympathetic interest. Most Soviet psychiatrists believe in an unconscious, albeit different from the Freudian concept, and an international psychiatric conference on the unconscious was held in Tiflis in 1979, with many Western and American psychoanalysts in attendance.

In the new atmosphere psychoanalysis is likely to receive more attention, but it is questionable whether it will ever attract much of a following. It is much too time-consuming to fit into socialized medicine, and Russian psychiatry traditionally has always remained close to medicine and the severe psychotic disorders, which even Freud regarded as biochemical in nature, leaving problems of character and personality to novelists and pedagogues or to the corrective influence of social criticism. The late Professor Popov of Moscow said to me long ago, "When a man quarrels with his wife, you American psychiatrists regard it as a disease; we regard it as a misfortune."

JOSEPH WORTIS, M.D.
Brooklyn, N.Y.

Occult Thyroid Dysfunction in Refractory Depression

SIR: An article by George R. Gewirtz, M.D., and associates (1) suggested the interesting possibility of using resting metabolic rate to detect occult thyroid dysfunction for the purpose of treating refractory depression with thyroxine. I would like to comment on some of the pitfalls of using this methodology.

Leaving measurement accuracy aside (2), the important question is, What is a "normal" resting metabolic rate, especially if it is used as a benchmark for detecting subtle thyroid dysfunction? The authors justified the use of thyroxine on the basis of finding resting metabolic rates between 7.7% and 17% below "normal." However, there can be a 20% to 30% variation in the rates of normal individuals with the same body composition (3). Furthermore, the standards used by the authors were questionable, since they were derived from a 1916 study of six men, 75-85 years old, with medical complications. A particular problem in determining standards is how to adjust for differences in body size. I have shown that "correcting" resting metabolic rate for body size by dividing by surface area can lead to errors ("The Comparison of Metabolic Rates When Body Size Differs," unpublished manuscript, 1988). Also, it should be noted that the authors incorrectly stated the formula for calculating surface area, which should read $71.84 \times \text{weight}^{0.425} \times \text{height}^{0.725}$ (2).

The interactions among three systems—thyroid function, metabolic regulation, and mood regulation—are complex (4). One must consider the possibility that resting metabolic rate may be altered in depression independently of changes in thyroid function (4). Patients can have hypothyroidism and major depression at the same time or have either alone, and resting metabolic rate may be altered for either reason or perhaps from another source (4). A complete thyroid evaluation must be made to interpret the data. The authors failed to do this.

T_3 levels were not reported. (T_3 resin uptake is a measure of thyroid-binding globulins and has nothing to do with T_3 levels per se.) T_3 , not T_4 , is the primary metabolically active

form of the hormone. T_3 levels have been reported to be low in depressed patients even when T_4 is high or normal (4). Resting metabolic rate can be low in depression because of decreased caloric intake. T_3 levels will reflect this and help distinguish between primary hypothyroidism and intake changes (4).

In addition, thyroid-releasing hormone (TRH) stimulation tests were apparently not done. Two of the authors' five patients who responded to thyroxine had normal levels of thyrotropin (TSH). This test can pick up grade 3 hypothyroidism when T_3 , T_4 , and TSH levels are normal (5). Resting metabolic rates might not have been needed to show hypothyroidism.

The other three patients who responded to thyroxine had elevated TSH levels (grade 2 hypothyroidism [5]), and two of these showed normal TSH levels when their "depression" resolved. Depressive symptoms may have lifted, but what probably resolved was the hypothyroidism. This is not semantic quibbling. Hypothyroidism and depression are separate illnesses, albeit with significant interactions.

The authors have brought further attention to an important area: the physiologic concomitants of psychopathology. Measuring resting metabolic rate may prove to be useful in the treatment of depression, but careful attention must be paid to standards of procedure, interindividual comparisons, and clinical assessment.

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JONATHAN ZACH, M.D., PH.D.
White Plains, N.Y.

SIR: In their report, Dr. Gewirtz and colleagues suggested that the assessment of metabolic rate was useful in the evaluation of refractory depression in a group of 15 women. They found that a subgroup of these patients had either elevated TSH levels or metabolic rates below published norms and that this subgroup generally responded well to the addition of thyroid hormone. They concluded that "it is clear that these patients suffered from some sort of occult thyroid disease, perhaps involving blunted tissue response to circulating thyroid hormone." While we agree that this represents a very reasonable hypothesis to propose and test, the report fell short of providing evidence one way or the other.

First, how can the authors explain the rather dramatic dissociation between TSH levels and metabolic rate? While we agree that the thyrotropes themselves may conceivably be subsensitive to the effects of thyroid hormone, and there is a pathophysiologic precedent for such a disease mechanism (1), why would some patients with low metabolic rates have TSH levels in the normal range (patients 1 and 5) while others had TSH levels above the normal range (patients 2, 3, and 4)?

Second, the authors seem to have acted on their hypothesis

before it was proven and selected for treatment with thyroid hormone primarily those patients who they felt had "occult thyroid dysfunction." Granted, some of those patients did indeed do well, but we have no way of knowing whether the other patients (who presumably showed no evidence of occult hypothyroidism) would have responded equally well to thyroid hormone treatment.

In the text, patient 5 is said to have had "an elevated TSH level," while in table 1, it is shown as 0.7 mIU/liter. Was this a typographical error?

We realize that the authors presented only their preliminary observations and that systematic study is to follow. However, we do object to the premature conclusion that these patients responded to thyroid medication because they had some type of thyroid disorder or a disorder of thyroid responsiveness. What the authors *have* shown is that thyroid medication may be useful in the treatment of refractory depression, a conclusion long recognized from other studies (2, 3). What the authors have *not* shown is that the measurement of TSH or metabolic rate can serve as a clinically useful predictor of this response.

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MURRAY B. STEIN, M.D., F.R.C.P.(C)
THOMAS W. UHDE, M.D.
Bethesda, Md.

Dr. Gewirtz and Colleagues Reply

SIR: We agree with Dr. Zach that the use of published normal standards for metabolic rate is problematic. Ideally, studies measuring metabolic rate should include metabolic studies of a control group for comparison. However, our study was designed as an open trial; although we used normal standards, metabolic rate still appeared useful in managing certain patients with refractory depression.

T_4 levels were reported in our study because a reduced serum T_4 level is most commonly found in early, mild hypothyroidism—usually with a normal serum T_3 level. In addition, although T_3 is the active hormone in determining metabolic rate, T_4 appears to have a significant role in feedback regulation of TSH secretion and, perhaps, in other areas of the brain (1).

TRH stimulation tests on patients with low metabolic rates would be interesting to obtain. The results would indicate whether or not this actually duplicates information obtained by metabolic rate assessment.

We apologize that our manuscript contained an error in stating the formula we used for calculating surface area. Body surface area was calculated according to the following formula: body surface area (cm^2) = weight (kg) $^{0.425}$ × height (cm) $^{0.725}$ × 71.84.

Drs. Stein and Uhde raise a number of salient points that

are important to address. Our study showed that certain patients with refractory depression had evidence of subtle thyroid dysfunction, demonstrated by low metabolic rate and/or elevated TSH, although levels of circulating T_3 and T_4 were normal. We hypothesized that these patients would particularly benefit from thyroid medication and that monitoring metabolic rate and TSH level might aid in their clinical management. Five of the patients with evidence of thyroid dysfunction had a clear response to thyroid supplementation. In addition, metabolic testing appeared to be helpful in determining doses of thyroid medication. However, this was an open investigation, not a controlled study; our conclusions were therefore clearly labeled as tentative.

It is interesting that two of our patients had low metabolic rates but normal TSH levels. While these data are intriguing, we can only speculate on the reasons for this finding. Perhaps, in these patients, the pituitary thyrotropes were more sensitive to thyroid hormone than end organs that affect metabolic rate. Patient 5 is interesting in this regard. Before she presented to us for metabolic testing, she had an elevated TSH level of 9.1 mIU/liter, although results of other thyroid function tests were normal. Her depression responded to desipramine and thyroxine (175 μ g/day). However, she was referred for metabolic testing due to concern that she had iatrogenic hyperthyroidism. Her metabolic rate while taking thyroxine was slightly low (-8.5%); interestingly, her TSH level at that time was normal (0.7 mIU/liter) (not a typographical error). Apparently, the addition of this dose of exogenous T_4 (thyroxine) was sufficient to normalize her TSH level, but her metabolic rate was low.

We are sure that Drs. Stein and Uhde are well aware that not all studies support the use of thyroid medication as helpful for refractory depression. We merely suggested the possibility, clearly justified by our reported experience, that some laboratory testing which is not usually considered may prove helpful in this regard.

To our knowledge, this was the first study to report the use of metabolic testing as an aid in the treatment of refractory depression. We agree that further investigation is needed to determine whether low metabolic rate and elevated TSH level can predict which patients with refractory depression will respond to thyroid supplements. Our study did not address the question of whether patients with normal TSH and metabolic rates respond equally well to thyroid medication. Indeed, we are currently conducting trials to answer this very question.

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GEORGE R. GEWIRTZ, M.D.
JACK M. GORMAN, M.D.
JULIE A. HATTERER, M.D.
New York, N.Y.

Deficit or Negative Syndrome?

SIR: William T. Carpenter, Jr., M.D., and colleagues (1) proposed that a deficit-nondeficit subclassification of schizophrenia is more meaningful (i.e., a more valid approach) than the positive-negative distinction. Their premise is that negative symptoms, reflecting a more severe etiopathic pro-

cess in schizophrenia, must not be confounded with manifestations secondary to depression, drug side effects, or positive symptoms. This point is well taken and fundamental to construct validity. We are not convinced, however, that their concept of deficit syndrome resolves this problem or that they have marshaled any evidence that it has greater validity than the positive-negative concept.

Although their criteria for schizophrenia with deficit syndrome instruct one to disregard negative symptoms associated with depression, adverse drug reaction, and other artifacts, Dr. Carpenter and associates provided no guidelines for this determination. Further, the negative symptoms are undefined, and their severity is not taken into account. A patient with minimal signs of two negative symptoms, for example, is judged as equivalent to a patient with profound deficits on five parameters.

According to Dr. Carpenter and his associates, a key advantage of their deficit concept is the longitudinal view: they suggest that a primary negative syndrome can be recognized by its stability over 12 months. It is possible, however, that depression, long-term drug effects, environmental deprivation, and unremitted positive symptoms can lead to sustained diminution of social and emotional functioning. More important, we see no empirical basis for presupposing that primary negative symptoms are stable across this extended period. Drug studies (2, 3) tend to concur that negative symptoms generally improve, even if less dramatically than positive symptoms. Our 2-year follow-up of acutely ill schizophrenic patients (4) casts doubt on the stability of either positive or negative symptoms in this early phase of illness. The observation by Dr. Carpenter and colleagues that there was a sustained deficit syndrome in only 14.6% of their schizophrenic outpatients underscores this lack of stability. The assumption that there exists a true set of immutable deficit features clearly remains to be tested rather than built into a scale.

The authors' finding of greater stability of negative symptoms in the deficit group than in the nondeficit group is not revealing, since the groups were selected on this basis, and it is not indicated that raters were blind to the patients' classification. It is interesting, however, that no difference in the stability of blunted affect was obtained. The only evidence of validity was the overrepresentation of males and the poor prognostic scores in the deficit group. Yet these findings are not particular to the deficit-nondeficit categorization; they have been reported rather consistently for the positive-negative distinction (5, 6). Indeed, from investigations using an operationalized rating scale, we found (6) that the validity of the positive-negative syndrome was supported by differences in sex, education, cognitive developmental tests, premorbid adjustment, family history of psychiatric illness, drug response, and outcome at 2-year follow-up.

We would suggest, therefore, that global longitudinal ratings are no more valid than standardized cross-sectional assessment of positive-negative syndromes for delineating separate processes in schizophrenia. By their very nature, such ratings are prone to confounding from variability over time, and they provide neither a necessary nor a sufficient basis for ruling out secondary negative symptoms.

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STANLEY R. KAY, PH.D.
LEWIS A. OPLER, M.D., PH.D.
New York, N.Y.

Dr. Carpenter and Associates Reply

SIR: Drs. Kay and Opler raise several concerns regarding the concept of deficit-nondeficit schizophrenia as a conceptual refinement over the positive-negative symptom distinction. Several of these (i.e., insufficiently operationalized criteria for defining key negative symptoms or for determining when negative symptoms are secondary to other factors) are not fundamental criticisms of the concept but simply reflect issues to be addressed if the deficit concept becomes an object of further investigation. Clinicians must presently make such distinctions in order to properly treat patients with negative symptoms (1).

The concern that our definition of deficit schizophrenia neglects quantification of severity of negative symptoms ignores the underlying premise that the distinction between deficit and nondeficit forms of schizophrenia is categorical. We and others have published reliable scales for quantifying negative symptoms.

The objection that negative symptoms secondary to factors such as depression or medication can also endure more than 12 months shows a misunderstanding of our proposed criteria. Duration and etiology (i.e., primary and secondary) are independent criteria. Both sufficient duration and the judgment that negative symptoms are primary are necessary for deciding that the deficit form of schizophrenia is present. Duration itself does not argue that secondary factors are absent.

It is ironic that Drs. Kay and Opler's data showing instability of positive and negative symptoms over time is offered as an argument against the deficit concept. Indeed, it is a basis for proposing the concept. The question is whether a subset of patients with primary, enduring negative symptoms is distinguishable from patients with nondeficit schizophrenia on important factors such as etiology, pathophysiology, and treatment.

Finally, the fact that some evidence for the validity of the positive-negative distinction already exists is not an argument that the concept could not benefit from further refinement. Obviously, the benefit of introducing the deficit concept can only be assessed from empirical work yet to be done, but perhaps this work will be more informative if investigators pay close attention to psychopathologic concepts and distinguish various sources of symptoms. For studies of etiology, for example, the positive-negative dichotomy has formidable conceptual problems. All schizophrenic patients must have had positive symptoms to meet the diagnostic

criteria. The positive-negative dichotomy depends in part on how severe the positive symptoms are on the day of assessment. The negative side of the equation will be polluted if the primary-secondary distinction is not made.

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WILLIAM T. CARPENTER, JR., M.D.
DOUGLAS W. HEINRICHS, M.D.
ALTHEA M.I. WAGMAN, PH.D.
Baltimore, Md.

Imipramine and Clonazepam for Panic Disorder

SIR: Bernard D. Beitman, M.D., and Lyle Clark, M.D. (1) referred to the fact that imipramine appears to trigger panic symptoms in some individuals. This phenomenon is well-known clinically; Klein et al. (2) reported that 10%-20% of patients with panic disorder are extremely sensitive to imipramine, reacting with extreme tension and insomnia, and that treatment may have to be instituted with very small doses, 3-10 mg. I have frequently observed a similar pattern with both imipramine and clomipramine. Patients with panic symptoms seem particularly prone to develop increased arousal, jitteriness, anxiety, and panic symptoms. A considerable percentage of patients cannot tolerate these medications and find such treatment problematic.

As an alternative in the pharmacotherapeutic component of treatment, clonazepam appears to be dramatically effective (3). However, it carries with it the disadvantages of the benzodiazepines. In particular, like other benzodiazepines, it can cause substantial depression or worsening of existing depression, including the development of suicidal ideation in certain cases. One solution to this problem is to use a combination of imipramine and clonazepam in the early stages of treatment. The clonazepam blocks the panic during the initial stages while tolerance to the side effects of imipramine is developed. Later, the clonazepam can be withdrawn.

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ALAN B. EPPEL, M.B., F.R.C.P.(C)
Guelph, Ont., Canada

Drs. Beitman and Clark Reply

SIR: We appreciate the suggestions about treatment of patients with panic disorder, but it seems that Dr. Eppel has overlooked the fact that our depressed patient did not report any previous symptoms consistent with panic during the initial interview or at follow-up. If the suggestion is that all patients treated with antidepressants be prophylactically

treated with benzodiazepines, this appears to be exposing the patient to risks of sedation and withdrawal that are unwarranted.

When treating panic, the clinician may be guided by the patient's history of sensitivity to other medications and may begin imipramine at either 10 mg or 25 mg and progress to the standard dose of 150 mg by raising the dose slowly at first and then more rapidly in the later stages. Clonazepam, alprazolam, and some other benzodiazepines certainly have their place in the treatment of patients who need immediate relief from the often devastating effects of panic disorder, and they may be sufficient as a single treatment. Some have suggested, as does Dr. Eppel, starting the antidepressant and benzodiazepine together and then withdrawing the benzodiazepine when the antidepressant has "kicked in." We tend to use one medication at a time, reserving the combination for the more treatment-refractory patients with either severe panic attacks or severe panic *and* major depression.

Unfortunately, the debate about whether to use an antidepressant, a benzodiazepine, or both ignores the likelihood that withdrawal of medication will lead to relapse. In an unpublished study by Sheehan (noted by C. Lewis, personal communication, 1988) more than 60% of panic disorder patients taking imipramine, alprazolam, or phenelzine relapsed within 6 months after discontinuing medication. Furthermore, people taking antidepressants are very likely to continue to take them for many years (1), sometimes because they fear relapse. New evidence is beginning to suggest that approximately 15 sessions of focused psychotherapy for reasonably well-functioning patients with panic attacks is more likely to prevent relapse (2). Perhaps the treatment combination should be one medication plus panic-focused psychotherapy.

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BERNARD D. BEITMAN, M.D.
LYLE CLARK, M.D.
Columbia, Mo.

S. Weir Mitchell's Early Fictional Description of Multiple Personality

SIR: The Sally Beauchamp case, probably the best known classic account of multiple personality, was published by Morton Prince in 1905 as *The Dissociation of a Personality*. Interest in such personalities has been traced back to at least 1811 in the United States and was reflected in a lecture by Benjamin Rush, but multiple personality was recognized elsewhere even before that date (1). Recent publications, including one by Bliss (2), reveal considerable attention to such patients.

S. Weir Mitchell (1829-1914), distinguished neurologist, neuropsychiatrist, and literary figure, in his novel *Dr. North and His Friends* (3) published in 1900, described the character Sibyl Maywood as a case of hysteria. I believe she was mistakenly called a multiple personality by Quinn (4), among others. She experienced brief episodes of dissociation, with amnesias reflecting repressed romantic feelings toward another

character in the novel but with no elements of a distinctly different type of personality. In 1891, however, Mitchell's novel *Characteristics* (5) was published, and in it is an account of unquestionable multiple personality. This case may perhaps be the first fictional description of dual personality, and it is surely one of the earliest. Multiple personality and dual personality have long been traditional diagnoses. The dual personality of J.C. in this novel would now be labeled "psychogenic fugue" according to *DSM-III-R*.

J.C., "a man of refined and scholarly tastes, a student of Oriental languages, failed in business." He was gentle, attached to his wife and child, and generally content. His wealthy wife gave him a large sum of money to pay his last debt in another city, his "one burden which had troubled a life otherwise entirely happy." He left home and disappeared. When found by his wife, J.C. had married again, having lost all memory of his previous life. He had another name. Slovenly in dress and unclean in person, he was "unpopular by reason of an abrupt temper." He was unsociable and morose but "clear-headed" and worked as a clerk in a dry-goods house. His first wife consulted a lawyer, who arranged to have both of them come to his office; her identity was not disclosed. J.C. had been absent 7 months. He did not recognize his first wife at the lawyer's office and said he had never heard of a man named J.C. Four months later he suddenly forgot the events of the preceding 11 months and appeared at his original home "in great perplexity and terribly disturbed," surprised at his own "rough dress" and once more "the quiet, well-bred, sensitive scholar." His second wife was told that he had a "disordered mind" and accepted from the first wife a generous financial settlement. J.C. asked his first wife "uneasy questions as to his presumed illness and long loss of memory." She protectively replied that for a long time vain efforts had been made to find him. "At last he showed a strong disinclination to hear his former mysterious condition referred to."

Mitchell did not stress J.C.'s apparent sense of guilt and self-punitive reaction to his financial failure and his reliance on the monetary assistance of his wife as partial causes of the dissociation, but he discounted current neurological explanations based on "our having two hemispheres in the brain."

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JEROME M. SCHNECK, M.D.
New York, N.Y.

Immune Function in Psychogenic Depression

SIR: We read with interest the article "Life Events, Depressive Symptoms, and Immune Function" by Michael Irwin, M.D., and colleagues (1). The authors studied two indicators of immune function, natural killer (NK) cell activity and measures of T cell subpopulations, in 37 women who dif-

ferred in the magnitude of their distressing life experiences. Severity of depressive symptoms in these women was associated with an impairment of NK cell activity, an absolute loss of suppressor/cytotoxic cells, and an increase in the ratio of T helper to T suppressor/cytotoxic cells.

To evaluate the correlation between depressive symptoms and immune impairment, we studied some parameters of immunity in a group of patients who developed depressive symptoms in various psychogenic situations. In each case, the extent of the expression of disorder was determined by the psychogenic state, depending on the psychotypological peculiarities of the patient.

Seventy-three patients with psychogenic depression, aged 18–51 years, were investigated on admission to the hospital, before they underwent psychopharmacotherapy. Blood samples from 40 mentally and physically healthy donors served as the source of control data. The changes we discovered in the patients were as follows: T suppressor cell reduction (mean±SD=11.7±1.15 in patients and 16.1±1.29 in healthy donors; $p<0.001$), decreased number of B-lymphocyte immature forms (mean±SD=7.6±0.47 and 11.37±1.01, respectively; $p<0.001$), elevation of the serum immune complex (mean±SD=103.5±5.76 and 79.2±6.55, respectively; $p<0.01$), and a tendency toward an increase in IgG. It is also necessary to note that the severity of the immune disorders correlated with the severity of depression.

In conclusion, the findings presented by Dr. Irwin and colleagues and our own data indicate definite abnormalities of the immune system in depressed persons. Thus, the detected changes in immune function may depend more on a universal neuromodulation mechanism than on psychogenic factors connected with social, geographic, and other environmental conditions.

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OLYMPIADA A. VASILJEVA, PROF., D.SCI.
NIKOLAJ A. KORNETOV, M.D., PH.D.
ALEXANDER I. ZHANKOV, M.D., PH.D.
VADIM I. RESHETNIKOV, M.D.
Tomsk, USSR

Dr. Irwin Replies

SIR: The findings reported by Prof. Vasiljeva and colleagues of decreased numbers of T suppressor cells and increased levels of serum immune complexes in depressed patients are in agreement with our observations of changes in T cell subpopulations during bereavement. In addition, clinical depression and depressive symptoms associated with stressful life events are associated with alterations in parameters of cell-mediated immune function, including reduced natural killer cytotoxicity (1) and decreased lymphocyte responses to mitogenic stimulation (2).

Neuromodulation of immune function is likely to underlie the association between psychological states and altered immunity. For example, corticotropin-releasing factor (CRF), which is increased in the CSF of depressed patients, elicits an array of hormonal, metabolic, circulatory, and behavioral changes that correspond closely to those seen in animals responding to stress. Recently, my associates and I presented

an animal model to demonstrate that central CRF can coordinate autonomic responses to modulate immune function (3). Central, but not peripheral, doses of CRF have been found to activate the autonomic nervous system and reduce splenic natural killer cytotoxicity in rats (4). Furthermore, activation of the pituitary adrenal axis is dissociated from changes in splenic cytotoxicity. While the sympathetic nervous system has been implicated in the regulation of immune function, these data provide direct evidence of the role of the brain in the neuromodulation of immune cells and have the potential for clarifying the link between depression and altered immunity.

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MICHAEL R. IRWIN, M.D.
La Jolla, Calif.

Unilateral ECT: Medications and Monitoring

SIR: As the use of ECT has been refined in recent years, attention to technical aspects, such as electrode placement and monitoring the duration of seizures, has assumed increasing importance in ensuring a successful outcome. These issues were alluded to but not resolved in the case described by Sudharam Idupuganti, M.D., and Raul Mujica, M.D., in their letter to the Editor (1). A young catatonic patient, after failing to respond to seven unilateral ECTs (six right, one left), showed slight improvement after five subsequent bilateral treatments. Of particular interest was the occurrence of unilateral peripheral autonomic signs on the side of electrode placement.

Drs. Idupuganti and Mujica were surprised that their patient did not exhibit a central autonomic response to ECT. The most common cause of this phenomenon is iatrogenic—the pre-ECT parenteral administration of the central anticholinergic agent atropine. Was this not done in this case, or was a peripherally active anticholinergic that does not cross the blood-brain barrier, such as glycopyrrolate, used instead? As mentioned in a review by Elliot et al. (2), the introduction of anticholinergic premedication has enhanced the safety of ECT by reducing bronchial secretions and preventing bradycardia and vagotonic arrhythmias.

Alternatively, the effects of the unilateral ECT in this patient may not have generalized across the midline, an apparently not uncommon occurrence that has fueled criticism of this treatment modality (3). If this lack of spread of autonomic activation were paralleled by a restriction of seizure activity to the side of unilateral electrical stimulation, the treatment might well fail to be effective (4). It is for this reason that monitoring the duration of generalized seizures has assumed an integral role in the administration of modern ECT. Unfortunately, the description provided by Drs. Idupuganti and Mujica

puganti and Mujica suggests limitations in their observations. Their only reference to seizure monitoring is to the presence (duration not stated) of visible seizure activity in the cuffed left upper arm of the patient during her first right unilateral ECT. However, positioning of the cuff *ipsilateral* to the electrode placement is necessary for maximal information in unilateral ECT (94). That is, seizure activity documented on the *right* side in this patient would have indicated that the electrical stimulation over the right hemisphere had spread across the midline to the left motor cortex, confirming a generalized seizure. While the relative efficacy of unilateral and bilateral ECT remains in some dispute, evidence suggests that, for at least some patients, careful monitoring of the duration of seizures (with restimulation when necessary) can yield a response rate to unilateral treatment (in which adequate seizure induction may be more difficult) comparable to that in bilateral ECT (5).

A final caveat about the reported case concerns the lack of diagnostic precision in what are described as "catatonic symptoms." Since it is now recognized that many catatonic states are associated with mood disorders—mania, in particular—the rationale for considering ECT early in treatment planning is strengthened; data from Small et al. (6) indicate a superiority of bilateral over unilateral ECT for the treatment of mania, as was true in this case.

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MATTHEW V. RUDORFER, M.D.
Bethesda, Md.

Drs. Idupuganti and Mujica Reply

SIR: We agree with several of Dr. Rudorfer's comments, especially about the diagnosis of our 16-year-old patient and the superiority of bilateral over unilateral ECT. Our letter was not intended to describe the technical parameters of ECT or to be a discourse on the syndrome of catatonia; we agree with Dr. Rudorfer that catatonia is associated with mood disorders as well as schizophrenia and wish to point out that we never said in our letter that the patient was schizophrenic. We were also unable to report certain technical details of our patient's treatment, such as the duration of seizures, due to the space limitations in letters to the Editor.

Failing to grasp that any medication given parenterally would circulate equally into both cerebral hemispheres, Dr. Rudorfer asks whether an anticholinergic medication such as atropine was used before we gave ECT to our patient, implying that the agent would have caused only one-half of the

face to flush—a pharmacological impossibility! Yes, we did pretreat our patient with atropine sulfate, 0.4 mg i.m., one-half hour before ECT. We must reiterate that in our literature search on ECT as well as in our collective experience of administering over 500 unilateral treatments, we had never before witnessed the phenomenon we reported, atropine or no atropine.

Dr. Rudorfer correctly points out, however, an error in our report; it is our practice to monitor seizure activity by applying a tourniquet to the ipsilateral, not contralateral, arm during unilateral ECT. We did monitor our patient's *right*, not left, arm during the administration of right unilateral ECT. We regret the error.

SUDHARAM IDUPUGANTI, M.D.
RAUL MUJICA, M.D.
Brooklyn, N.Y.

Ethical Concerns About New Socioeconomic Trends in Mental Health Care

SIR: "Privatization of Psychiatric Services" (1), a report of a study supported in part by an NIMH grant, was written within very narrow parameters, leaving unmentioned the realities of supply-side economics (so popular these days) and the effects on all aspects of health care provision. It is not enough that mergers and takeovers net banks, financial entrepreneurs, and attorneys hundreds of millions of dollars while the taxpayers are required to rescue the thrift institutions. Lately, we have seen hospitals spend hundreds of thousands of dollars on advertising while they claim to be unable to care for the indigent or to acquire necessary primary care equipment (2).

As far as psychiatrists are concerned, we still have the spectacle of these specialists owning and operating private psychiatric hospitals, as if there were no such thing as conflict of interest, and those who, upon any referral for treatment, book a bed in the hospital, provided the patient has reasonable insurance coverage.

In the *Journal* issue in which the article on privatization was published, a letter to the Editor by Marvin H. Lipkowitz, M.D. (3) mentioned residents feeling that "a dearth or surplus of psychiatrists should be evaluated on the basis of patients' needs rather than psychiatrists' incomes"; Dr. Lipkowitz said "in their defense" that they are "all young and naive." He also feels that "the morality of . . . [supply-side economics] is beside the point." I would suggest that it is exactly the point at which we, as noneconomists but as physicians concerned with human health and well-being, can and probably should stand up and be counted. Privatization may be of economic interest, but in our profession it should be the business of ethics committees.

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EDWARD A. NOL, M.D.
Birmingham, Mich.

Drs. Dorwart and Schlesinger Reply

SIR: Dr. Nol is correct in stating that in our article on privatization we deliberately attempted to present a balanced overview of the topic. As health policy researchers, we are concerned with problems and issues that can be stated clearly and then studied feasibly by data-based methods. Currently, there is a shortage of good studies and available data concerning access, quality, and costs of psychiatric services. We agree that there are also public policy and professional practice dimensions to privatization that we did not discuss in our paper; however, it was not our intention to do so.

For a more detailed discussion of the public policy implications of the privatization of psychiatry that concern Dr. Nol, we can refer to some recent discussions; one is the editorial by Steven S. Sharfstein, M.D. (1) in the same issue as our article. He observed that "access to psychiatric care by the poor . . . may become more acute in the years to come." He also suggested that "as clinician-leaders, psychiatrists must play an active role in this public and private policy debate, since its outcome will determine future professional practice and the availability of treatment." As for ethical concerns, these have recently been reviewed in a thoughtful discussion by the APA Ethics Committee (2). The committee notes the problems raised by physician ownership of facilities and equipment, the potential for inequities or abuse in for-profit operations, and several kinds of threats to the doctor-patient relationship resulting from the "double agent" role imposed on physicians by some forms of organization and reimbursement of psychiatric services.

To be sure, there are many people who share Dr. Nol's concern about the effects of privatization on psychiatric services and who also question the role of physicians in such activities as policy research, policy making, and health management. An insightful commentary on the dilemma of the psychiatrist in an increasingly competitive and "corporatized" world was given by Dr. Barry Blackwell at APA's 1988 annual meeting in Montreal (discussion of Paper Session 42 on Quality of Care in Psychiatry). Indeed, there are many aspects of professional practice that are influenced by economic trends, but privatization is not the only major socioeconomic trend in mental health care. Other trends, such as medicalization, subspecialization, changing reimbursement (e.g., capitation, relative value scales), and regulation, are also exerting major influence. We believe that further research on mental health services with respect to these topics, including their impact on psychiatric care, is both necessary and desirable. Such research should be multidisciplinary and involve clinicians as well as economists, policy analysts, and other social scientists.

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ROBERT A. DORWART, M.D.
MARK J. SCHLESINGER, M.D.
Cambridge, Mass.

Videotape Recording of Assaultive Inpatients

SIR: We understand the need for scientific studies of violence as highlighted by the use of videotape recording of inpatients. However, we notice a number of clinical, legal, and ethical conundrums that the study by David A. Brizer, M.D., and associates (1) appears to raise.

It is curious that the ward staff "expressed concern about being videotaped." We are only left to speculate on the nature of the staff's reservations about being filmed. If "normal" individuals have reservations about being observed, we wonder what paranoid inpatients think. The issue of informed consent for videotaping was not discussed. Considering that the patients who were videotaped were characterized as "too assaultive to be managed elsewhere in the hospital," it seems likely that their capacity to control their behavior was minimal and that their corresponding mental state would similarly reflect insufficient capacity for giving informed consent to be videotaped. At the very least, the issue of informed consent needs some discussion.

Beyond the informed consent issue is the parallel issue of the *Miranda* warning (2). We realize the civil (noncriminal) nature of psychiatric hospitalization. However, since hospital staff members assaulted by inpatients may be encouraged to seek criminal prosecution of the offending patients (3, 4), the legal system may have access to videotapes recording the alleged assaults, even though the videotapes are classified as "research data." If criminal prosecution is a possibility, not only informed consent but a true *Miranda* warning may be indicated.

While research by videotaping violent behavior of inpatients may serve to enhance our clinical understanding of these maladaptive behaviors, its Orwellian context may be ethically unacceptable in a democratic society. In conclusion, the clinical and, especially, the legal and ethical issues raised by this research project appear to warrant further examination before similar endeavors are undertaken in the future.

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GREGORY B. LEONG, M.D.
J. ARTURO SILVA, M.D.
Los Angeles, Calif.

Dr. Crowner and Associates Reply

SIR: We appreciate the legal and ethical concerns raised by Drs. Leong and Silva in response to the report on our project designed to better understand psychiatric inpatient assaults by using closed-circuit television cameras.

Drs. Leong and Silva raise two specific issues: obtaining informed consent to be videotaped and the possible use of videotapes in criminal proceedings initiated by staff members against patients. We will address each in turn.

We chose not to seek informed consent from the patients.

Institutional review board approval for a total waiver of the requirement for consent was granted because our project met all Federal requirements for such a waiver, namely, that the research will involve no more than minimal risk to the subjects, that the waiver will not adversely affect the rights and welfare of the subjects, that the project cannot practicably be carried out without the waiver, and that the subjects will be provided with additional pertinent information after participation when appropriate.

To be videotaped involves minimal risk to the rights of patients. The only conceivable risk would be invasion of privacy. To protect patients' privacy, all videotapes are stored in a locked office to which only a few research personnel have access. Only a few designated research personnel and ward staff are allowed to view tapes. No tapes may be removed from this office. Our hospital's quality assurance department has been designated by the institutional review board to ensure compliance with these patient safeguards, as it does with all research projects.

It would not be feasible for us to conduct this work if consent were required. Because there is only one specialized ward for violent patients at our facility, there would be no alternative ward for patients who refused consent. Instead, these patients would have to remain on wards where they had already proved themselves unmanageable and dangerous to staff and patients alike.

A main goal of this project is to collect information that may be useful to patients and staff. When the project is complete, additional information, such as what patient behaviors tend to be followed by assaults by peers, will be provided to patients.

It is not clear to us how the *Miranda* warning would apply to a situation such as this, where no one has been arrested. The camera system was not installed to incriminate staff or patients or to aid in anyone's criminal prosecution.

The patients on our specialized ward represent a small, highly atypical group of chronically assaultive and dangerous psychiatric inpatients. We believe that the small possible risk to these patients' rights should be considered in light of the possible benefits to all patients and clinicians who must risk bodily injury when exposed to assaultive inpatients. This project was designed to provide information that may help predict assaults and prevent further injuries.

MARTHA CROWNER, M.D.
ANTONIO CONVIT, M.D.
DAVID BRIZER, M.D.
JAN VOLAVKA, M.D., PH.D.
New York, N.Y.

Need for Geriatric Psychiatrists

SIR: I read with interest the article "Training in Geriatric Psychiatry: Will the Supply Meet the Demand?" by Gary W. Small, M.D., and associates (1). Anecdotal reports from fellowship program directors suggest that there is a dearth of applicants for existing fellowship slots rather than a need for an increased number of slots, as the authors contended.

In an earlier article (2), I argued against the simplistic use of ratios of psychiatrists to patients to justify an increased number of trainees. The same clearly applies to the arguments in this article. Data from the Epidemiologic Catchment Area study (3) indicated that fewer than 20% of persons over the age of 65 who have a Diagnostic Interview Schedule/DSM-III disorder make any mental health visits,

and of those, considerably fewer than one-half see mental health specialists, not all of whom are psychiatrists. Similar data from a neighborhood health center (4) also showed that "fewer than one-half of elderly persons with mental disorder diagnosis were seen in the specialty mental health unit, significantly fewer than other adults." Dr. Small and associates are correct that future cohorts of the elderly may be more willing to seek or accept psychiatric treatment than the present cohort. However, many older people will still prefer to discuss their problems with or receive psychotropic medications from their primary care physicians. That reality supports the authors' recommendations that better training in geriatric psychiatry be required in the general medical education and continuing medical education of nonpsychiatric physicians. Training in geriatric psychiatry is also a new requirement for accreditation of residency programs in general psychiatry.

I wholeheartedly agree with Dr. Small and colleagues that more attention to the mental health problems of the elderly will be demanded in the future. Medicare funding for outpatient psychiatric services has finally been increased from \$250 to \$1,100 a year for psychotherapy, and there is no limit for "medical management" of mental disorder. With increased demand from a growing and more psychologically sophisticated group of elderly persons who have improved insurance coverage, there should be an increase in the number of psychiatrists willing to provide services.

There are some hopeful signs. Geriatric psychiatry is becoming a respectable academic field, with a proposal for an American Board of Psychiatry and Neurology examination for added qualifications, the establishment of programs in geriatric psychiatry within many departments of psychiatry, the assumption of department chairmanships by geriatric psychiatrists, the frequent publication of articles on geriatric psychiatry in prestigious general interest psychiatric journals, and increases in research funds. The challenge for academic programs is to continue to expand the knowledge base and provide the necessary training for general psychiatrists as well as specialists in geriatric psychiatry.

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BENJAMIN LIPTZIN, M.D.
Belmont, Mass.

Drs. Small and Beck Reply

SIR: Dr. Liptzin makes some important points about the dearth of applicants for existing geriatric psychiatry fellowship programs and the relatively low percentage of elderly people currently receiving care from mental health specialists. Although findings from the 1984 Epidemiological Catchment Area Program confirm the low percentage of elderly receiving care from psychiatrists, the most recent data

available on ambulatory visits to various medical specialties indicate an increase in this percentage (1). An analysis of the National Ambulatory Medical Care Survey indicates that in 1978, 4.5% of total visits by ambulatory patients were to psychiatrists. This percentage has since risen to 6.5% in 1985 (1).

A critical roadblock to trainee recruitment not mentioned is the inadequate salary support for Fellows. Stipends from the National Institute of Mental Health provide only partial support, which is often uncertain until months or even days before fellowships begin, depending on available funding. Program directors rely on local institutional supplementation and other resources for fund raising—uncertain sources during these times of fiscal constraint. Potential trainees are understandably reluctant to commit themselves to 2-year positions that may or may not reimburse their time partially, if at all. Until our fellowships receive solid funding bases, the problem of recruitment will persist.

To what degree the dearth of geriatric psychiatrists explains the fact that only a fraction of elderly people currently receive care from mental health specialists is difficult to determine. Our own experience and that of our colleagues in geriatric psychiatry is that keeping up with referrals is nearly an impossible task. When colleagues and patients are aware of the availability of specialists, they seek them out.

The dearth of outstanding applicants for both geriatric medicine and geriatric psychiatry is becoming increasingly evident, with the most apparent gap between the supply and demand for academic geriatricians. The fact that training capacity is outstripping the supply of first-class trainees is one that requires national attention. Early exposure to geriatric content in medical schools, powerful role models, an established career ladder, and vigorous clinical and research programs will encourage quality applicants for geriatric training positions. Careful research is necessary to elucidate the reasons for the perceived unattractiveness of geriatrics and to identify additional strategies for removing barriers to the entry of quality applicants. There is also a need for a national educational strategy directed at increasing awareness about the opportunities in geriatrics, highlighting these in this new and emerging field, and demonstrating that geriatrics clearly makes a difference in the care of older persons.

In light of these observations and the estimated service need, we continue to argue for augmented fellowship support. Such expansion would lead to a greater number of specialists who would provide not only direct care but also academic support for the generalist.

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GARY W. SMALL, M.D.
JOHN C. BECK, M.D.
Los Angeles, Calif.

Effects of Diagnosis and Context on Dangerousness

SIR: I refer to the recent report of Renée L. Binder, M.D., and Dale E. McNiel, Ph.D. (1), who examined preadmission (within 2 weeks of hospitalization) and in-hospital (during

the first 24 hours) violence in a sample of 253 patients admitted to a short-term psychiatric unit. They found that 46% (N=117) had either engaged in fear-inducing behavior or had attacked a person before admission, and 45% (N=114) had done so during the first 24 hours of hospitalization. Before admission, both the manic patients and the schizophrenic patients had been significantly more likely to engage in violent behavior than the patients with other diagnoses. During the first 24 hours of hospitalization, only the manic patients were significantly more likely to be assaultive than patients in other diagnostic groups.

Coincidentally, I recently completed a somewhat similar study with quite different results. I evaluated all of the 34 patients (6.4% of the 533 admissions for one year) admitted to the psychiatric unit of a university-affiliated general hospital for a mandated assessment (Form I, Ontario Mental Health Act, Canada) because of actual or threatened violence (2). In the 48 hours before admission, eight subjects had assaulted another person, two had damaged property, and all had been verbally threatening. During the first 24 hours in the unit, only one patient was violent (e.g., she slapped a nurse), although 16 were intermittently noisy and threatening. Within 48 hours, the patients were indistinguishable in their behavior from the rest of the ward population. The average stay for the group was 12.4 days, which was less than the average for all psychiatric patients together (19 days), and the majority were discharged routinely to the community. Primary and secondary DSM-III psychiatric diagnoses were made within 24 hours of admission. Thirteen of the patients were psychotic (including nine with schizophrenia), and 21 were nonpsychotic (including six with adjustment reactions). The most common secondary diagnosis was personality disorder. In contrast to the findings of Drs. Binder and McNiel, the nonpsychotic patients were considerably more likely to have engaged in assaultive behavior before admission. In most cases, this took place in the context of an interpersonal crisis, which was often fueled by intoxication with ethanol (25%). Serum ethanol was assayed in three men and revealed levels of 212, 180, and 183 mg/100 ml.

Despite the high frequency of preadmission assaults and property damage (almost 30%) and threats, only one patient (a 66-year-old hypomanic woman) was violent in the first 24 hours following hospitalization. Possible reasons for the low rate of violence include 1) sobering up, with a concomitant reduced likelihood of violent acting out, 2) separation, consequent upon admission, from an aggravating person who had either triggered or escalated the violence, 3) the presence of a police guard for up to 48 hours following admission, which has been seen to have an inhibitory effect on aggressive acting out (3, 4), and 4) the preselection of patients before arrival (e.g., it is possible that unbeknownst to us, some more seriously ill psychotic patients were directed to the area's psychiatric hospital by the police or other agencies).

Despite the discrepancy between these two ostensibly similar investigations (notably, a much lower rate of violence in my study and different diagnoses associated with violence), when the results of the two studies are taken together, some tentative conclusions emerge. 1) Violence in nonpsychotic patients (with or without intoxication), in association with interpersonal conflict, is more likely to resolve quickly in the hospital, and 2) violence occurring soon after admission is likely to be perpetrated by psychotic patients (notably, manic ones) regardless of contextual variables.

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A.J. COOPER, M.D., F.R.C.PSYCH.
St. Thomas, Ont., Canada

Drs. Binder and McNeil Reply

SIR: We thank Dr. Cooper for his interest in our paper. In his sample of 34 patients admitted to the hospital because of actual or threatened violence, he found that nonpsychotic patients were considerably more likely to have been assaultive before admission, and during the first 24 hours after admission, only one patient was violent. Dr. Cooper's results differ from our findings, which indicated that before admission, schizophrenic and manic patients were more likely to be violent than patients with other diagnoses. During the first 24 hours of hospitalization, we found that manic patients were the most likely to be assaultive.

Dr. Cooper's study had methodological problems that limit the confidence which can be placed in his conclusions about the relationship between diagnosis and violence. First, he did not have a large enough sample of patients with each diagnosis. Dr. Cooper's sample consisted of 13 psychotic patients and 21 nonpsychotic patients. Of the 13 psychotic patients, nine were schizophrenic. Our sample was large enough for us to examine schizophrenic and manic patients separately. Our results showed that it is important to differentiate between specific psychotic diagnoses, since manic patients were more likely to be violent during the first 24 hours of hospitalization than patients with schizophrenia or other diagnoses. The only way that we were able to identify this pattern was by having adequate numbers of manic and schizophrenic patients. Second, Dr. Cooper did not take into account other well-known correlates of violence, e.g., age and gender (1), as possible reasons for the apparent association between violence and diagnosis. Our study took into account these potentially confounding variables. The same association between diagnosis and violence was found even when we controlled for these other variables.

As Dr. Cooper suggests, his setting was very different from ours. Only 6.4% of his patients were admitted because of actual or threatened violence. Also, 25% of them were intoxicated. In our community, nonpsychotic intoxicated patients are frequently admitted to a detoxification program or sent to jail rather than to an acute psychiatric unit. Our study was conducted on a short-term locked unit. The rates of violence we observed both inside and outside our hospital are quite similar to those found by other investigators who have studied similar settings (2-4).

Consistent with our findings, several large studies before ours (2, 5) found an association between psychotic diagnoses, particularly schizophrenia, and preadmission violence. Our finding of an association between mania and preadmission violence is new, but most earlier studies did not compare manic patients with others. Although one study has

replicated our finding concerning the increased risk of violence by acute manic patients during the initial period of hospitalization (J.C. Beck and J. Bonner, "Emergency Civil Commitment: Predicting Hospital Violence From Behavior in the Community," manuscript submitted for publication), further research on psychopathology and violence is needed. Our study indicates the importance of considering situational variables in such research.

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RENÉE L. BINDER, M.D.
DALE E. MCNIEL, M.D.
San Francisco, Calif.

Countertransference and Supervision

SIR: I am writing because of my difficulty in reconciling the perspective on privacy provided by R. William Betcher, Ph.D., M.D., and Norman E. Zinberg, M.D. (1) with my own experience. They seem to have been arguing that countertransference models of psychotherapy supervision and mechanical recording of therapy should be avoided to maintain a "narrow band of privacy." They presented a gestalt and examples of the countertransference model supervisors as unempathic, authoritarian overpathologizers. They seemed to emphasize countertransference as pathology in the supervisee and ignore how countertransference can be a vehicle for understanding the patient. Most countertransferences seen in supervision do not indicate pathology in the supervisee but are expectable and largely normal reactions to the patient's transference. When supervisors share their countertransference reactions toward the patient with the supervisee (as mine often did) and foster comparison of countertransference reactions followed by cognitive elaboration, the experience of invasion of privacy should be rare. The "parallel process" model can also be a vehicle for the supervisor to share personal reactions and thus clarify the "rhythm of the dance" that the patient leads.

Respect for privacy is an empathic function, and invasion of privacy indicates an empathic lapse. It should not be generally assumed that empathic lapses by supervisors are provoked by the model of supervision or the recommended method of conveying interactions that occur in therapy. I will not argue that observation does not influence the process of therapy. I am arguing that *who* does the observing or the quality of the trainee's relationship with the supervisor has more bearing than the method of observation or the model of supervision. Empathic supervision will mitigate adverse effects of observation on rhythms, concentration, and capacity

for undoing. The fact that mechanical recording and the countertransference model of supervision hold potential risk of misuse by marginally competent supervisors is no reason to argue against their use by all supervisors.

The authors' perspective could be translated into a hypothesis and be tested empirically by a variety of approaches. The anecdotes and surmise they presented should be subjected to a more controlled investigation to find out whether their opinions are substantiated and such broad conclusions are warranted.

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MARTIN A. WEILER, M.D.
Omaha, Neb.

Drs. Betcher and Zinberg Reply

SIR: We certainly agree with Dr. Weiler that our interest in privacy in psychotherapy and privacy in supervision requires more specific research than the interviews we reported in our paper. It is our hope to carry out such research in the near future.

Otherwise, we suspect that Dr. Weiler somewhat misunderstood the thrust of our argument. To the extent that too little attention has been given to the complex subject of privacy in psychotherapy and in supervision, we found that this lack of attention more readily lends itself to abuses in the so-called countertransference model. Also, borrowing from Wallerstein and Ekstein, we pointed out how its closeness to some models of psychotherapy makes that model attractive for inexperienced supervisors. At no point did we imply that supervision should be completely didactic and that there is no place in supervision for attention to countertransference. Rather, we stressed the importance of being aware of the potential for invasion of privacy when this important aspect of supervision is being considered. We agree that the skill, capacity for empathy, and experience of the supervisor are critical to the success of the supervisory process.

Furthermore, when we spoke of the didactic model we had no long-distance lecturing in mind. As we pointed out, the supervisory relationship is an extraordinarily complex one—with the teaching leavened by collegiality, sometimes friendship, and, certainly, personal experiences and anecdotes—in a way that therapy is not.

The same is true with respect to using mechanical aids for research. Both of us are entirely in favor of such procedures and participate in such work. It is as a result of such participation that we found it useful to remember that a Heisenberg effect takes place and that research, like supervision, changes the therapy situation in subtle but important ways.

R. WILLIAM BETCHER, M.D., PH.D.
NORMAN E. ZINBERG, M.D.
Cambridge, Mass.

Decision Making in the Emergency Room

SIR: Daniel C. Marson, J.D., and associates clearly set forth the advantages of multivariate over univariate analyses in their recent overview of psychiatric decision making in the

emergency room (1). We would add that the ultimate test of such decisions lies in the determination of *how the patients fare after the decision is carried out* rather than in the significance of the variables used in making those decisions.

In this connection, we regret that the authors did not review our article on this subject (2). Briefly, we selected three variables: the patients' dangerousness, support system, and motivation and ability to cooperate. These form the basis of a rating scale that is used to determine the admission decision. Our study differs from others in that after making the decision, we followed 122 patients (54 hospitalized and 68 not hospitalized) for a period of 6 months. A stepwise discriminant analysis of the three variables indicated that the use of all three variables to determine whether or not to hospitalize was far more discriminating for this purpose than was any single variable. Of even greater interest was the finding that except for two patients (one hospitalized and one not) who ended up in jail, there were no suicides, assaults, homicides, or other arrests during the study period.

We agree with Mr. Marson and associates that these days there is a wide range of possible outcomes. Our mobile crisis intervention service, which extends our emergency room and its decision-making ability out into the community (3), has available many alternatives to hospitalization. We prefer to treat the patient in the community if we can do so safely and effectively. Still, the crucial decision remains: whether to admit the patient for treatment against his or her will. We need to know how dangerous the person is, how much help (or opposition) to expect from the support system, and how well the patient can and will participate in treatment. Some variables (e.g., past hospitalization) contribute little. Others (e.g., diagnosis, severity of symptoms) bear importantly on the determination of dangerousness and ability to cooperate and are subsumed there.

It is of considerable interest and importance to be able to weigh the significance of the variables used by different individuals serving diverse populations with the resources available to them as they make decisions in the emergency room. Outcome studies can then determine the usefulness of the knowledge thus obtained.

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HERBERT BENGELSDORF, M.D.
LAWRENCE E. LEVY, M.D.
Valhalla, N.Y.

Mr. Marson and Dr. McGovern Reply

SIR: In their letter, Dr. Bengelsdorf and Dr. Levy state that the "ultimate test" of emergency room decision making is patient outcome following the referral decision, and they express regret that our recent overview of decision-making research did not include their own outcome study. While we agree that emergency room outcome studies are important,

we did not include such studies in our overview because we feel that they are analytically quite distinct from the decision-making studies.

The decision-making studies seek to uncover the primary determinants of emergency room disposition, in order to assess the rationality of the decision process in the emergency room. The decision-making studies thus reveal the underlying heuristics of the decision process, without considering whether "good" or "appropriate" referral decisions actually occur. Outcome studies, in contrast, address this very issue; that is, they seek to determine the long-term appropriateness of referral decisions by assessing subsequent patient outcome. The distinction parallels the one found in the psychotherapy research literature between studies which explore factors that influence the therapeutic process or interchange per se and studies which investigate the variables that contribute to positive (or negative) therapeutic outcomes (1).

With respect to the comments of Drs. Bengelsdorf and Levy, we find that both forms of inquiry yield "useful" knowledge, albeit of different kinds. The value of multivariate decision-making research is that it can clearly reveal the hierarchy of different factors, rational and irrational, which compel referral decisions. For example, one multivariate study of decision making at four Manhattan psychiatric emergency rooms (2) found that institutional factors—the specific staffing patterns and program alternatives at the different facilities—were the critical factors influencing the decision to admit. While not "useful" from the standpoint of justifying referral decisions or illuminating variables that contribute to eventual positive outcome, these findings have obvious relevance for hospital policy makers concerned about maintaining consistent admission standards and patterns of disposition among different facilities.

Although analytically distinct, emergency room decision-making research and emergency room outcome research obviously do share a close kinship, and together they serve the purpose of assisting hospitals in fashioning clinically and fiscally rational emergency programs. We are aware of a number of studies that have combined a clinical description of psychiatric emergency room patients with a follow-up assessment of outcome (3–5). As far as we know, however, no study to date has combined a thorough analysis of decision making with a follow-up assessment of outcome.

Finally, we do view the study of Drs. Bengelsdorf and Levy as an important contribution to research on the outcome of emergency room decisions. Their use of a brief checklist as a prospective screening instrument for prediction of the need for hospitalization represents an innovative approach to the study of outcome; its relative simplicity and speed of completion also possess obvious clinical value in the emergency room setting. However, given that their three checklist criteria were derived empirically, it might be useful to conduct an independent multivariate analysis to determine whether,

in fact, the three criteria correspond to statistically derived determinants.

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DANIEL C. MARSON, J.D.
MARK P. MCGOVERN, PH.D.
Chicago, Ill.

Our Changing Science

SIR: The following was overheard in the corridors of an academic neuropsychiatric center.

Psychiatrist A: An interesting schizophrenic patient. He loves cigars. When he lights one up, the negative symptoms disappear. He glows with pleasure.

Psychiatrist B: Perhaps cigar smoking has dopalytic activity.

Psychiatrist C (passing by): Sometimes a cigar is just a cigar.

Comment: Some things never change.

MICHAEL H. SACKS, M.D.
LISA DIXON, M.D.
New York, N.Y.

Correction

In the review by Edward M. Opton, Jr., Ph.D., J.D., of the book *Divided Staffs, Divided Selves: A Case Approach to Mental Health Ethics*, by Stanley Joel Reiser, Harold J. Buřstajn, Paul Appelbaum, and Thomas G. Gutheil (September 1988 issue, p. 1165), the statement "Hypothetical cases take up more than half of the text" is incorrect. On page 1 of the book reviewed the authors state, "The cases are real and are derived from clinical situations and consultative experiences of the authors, and their colleagues."

Reprints of letters to the Editor are not available.

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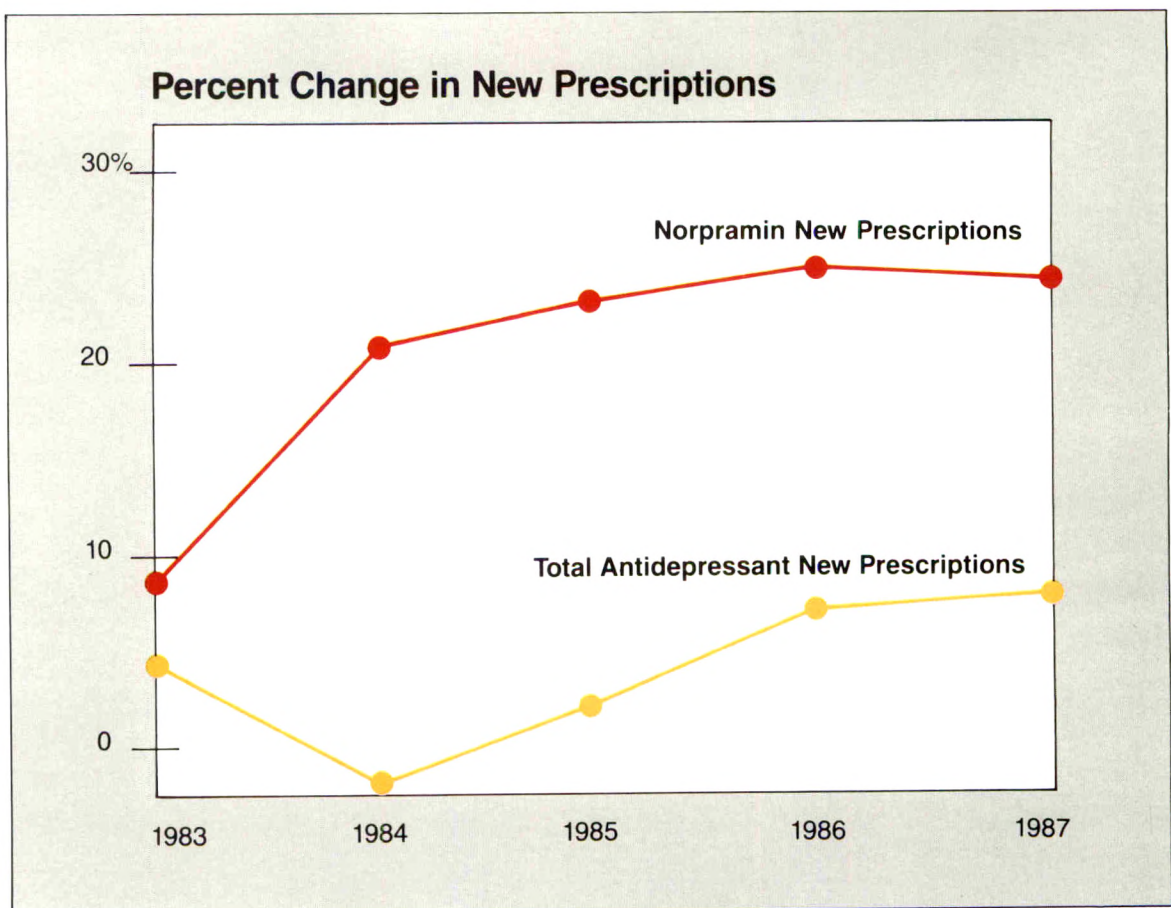


Figure 1. The red line tracks the percent change in new Norpramin prescriptions. The yellow line represents the total new

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(see Warnings)
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*Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

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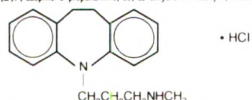
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CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid. While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake. Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine. The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-fold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke. Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug. Hypertensive crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:

- In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
- In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
- In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
- In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.

2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.

USE IN PREGNANCY

Safe use of desipramine hydrochloride during pregnancy and lactation has not been established, therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.

USE IN CHILDREN

1. Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.

5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.

2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.

4. The drug may cause exacerbation of psychosis in schizophrenic patients.

5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.

6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.

7. Clinical experience in the concurrent administration of ECG and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.

8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlorazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.

9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, Metabolism). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.

10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.

11. Both elevation and lowering of blood sugar levels have been reported.

12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia and nightmares, hypomania, exacerbation of psychosis.

Neurologic: numbness, tingling, paraesthesia of extremities, incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms, seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis, blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure, constipation, paralytic ileus, urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, photosensitivity, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, partial ejaculation, testicular swelling, elevation or depression of blood sugar levels, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function, weight gain or loss, perspiration, flushing, urinary frequency, nocturia, parotid swelling, drowsiness, dizziness, weakness and fatigue, headache, alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSEAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended. Dosage should be initiated at a lower level and increased according to tolerance and clinical response. Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECGs) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose. Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 75 to 100 mg daily. Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose. Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSEAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotensive shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperreflexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precept: early evacuation of the ingested material and subsequent support of respiration (airway and movement of circulation), and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal, releases may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dialyzable. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for full control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluid. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
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25 mg yellow coated tablets imprinted MERRELL 11 or NORPRAMIN 25
NDC 0068-0011-01: bottles of 100

50 mg green coated tablets imprinted MERRELL 15 or NORPRAMIN 50
NDC 0068-0015-01: bottles of 100

75 mg orange coated tablets imprinted MERRELL 19 or NORPRAMIN 75
NDC 0068-0019-01: bottles of 100

100 mg peach coated tablets imprinted MERRELL 20 or NORPRAMIN 100
NDC 0068-0020-01: bottles of 100

150 mg white coated tablets imprinted MERRELL 21 or NORPRAMIN 150
NDC 0068-0021-01: bottles of 100

Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect from excessive heat.

Product Information as of April, 1987

Merrell Dow Pharmaceuticals Inc., Subsidiary of The Dow Chemical Company, Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

Calendar

(Continued from page A18)

eral, 2006 Dwight Way #304, Berkeley, CA 94704; 415-845-7957.

May 6-7, annual meeting, American Association of Chairmen of Departments of Psychiatry, San Francisco. Contact Jeffrey L. Houpt, M.D., Secretary-Treasurer, Box AF, Emory University School of Medicine, Atlanta, GA 30322; 404-727-5881.

May 6-7, annual meeting, Black Psychiatrists of America, San Francisco. Contact Thelisa Harris, M.D., President, 664 Prospect Avenue, Hartford, CT 06105; 203-236-2320.

May 6-12, annual meeting, American Psychiatric Association, San Francisco. Contact Ms. Kathleen Bryan, Office of Meetings Management, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005; 202-682-6076.

May 11-14, annual meeting, American Geriatrics Society, Boston. Contact Linda Hiddeman Barondess, Executive Vice-President, 770 Lexington Avenue, Suite 400, New York, NY 10021; 212-308-1414.

May 12-14, annual meeting, American Society of Group Psychotherapy and Psychodrama, New York. Contact Stephen F. Wilson, A.C.S.W., Executive Director, 116 East 27th Street, New York, NY 10016; 212-725-0046.

May 13-17, 24th Annual Meeting and Exposition of the Association for the Advancement of Medical Instrumentation, St. Louis. Contact Anna Belousovitch or Debbie Tritle, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598; 800-332-2264 or 703-525-4890.

May 14-19, 25th Annual Meeting Congress, The Royal Australian and New Zealand College of Psychiatrists, Honolulu. Contact Conference Associates, 335 Moray Street, South Melbourne 3205, Australia; 03-699-3955.

May 20, annual meeting, Recovery, Incorporated (The Association of Nervous and Former Mental Patients), Chicago. Contact Mary Jane Maggio, President, 802 North Dearborn Street, Chicago, IL 60610; 312-337-5661.

May 22-24, 2nd World Congress on Chronic Rhoncho-pathy, Barcelona. Contact Secretaria Tecnica: BRP Barcelona Relaciones Publicas, Edificio Layetana, C/ Pau Claris, n. 138, 7^a 4^a, 08009-Barcelona, Spain; 93-215-7214

May 23-25, 35th Annual Meeting of the American Society for Artificial Internal Organs, Dallas. Contact ASAIO Annual Meeting, P.O. Box C, Boca Raton, FL 33429; 407-391-8589.

May 28-31, annual meeting, Association for the Care of Children's Health, Anaheim, California. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, 3615 Wisconsin Avenue, N.W., Washington, DC 20016.

May 28-June 1, annual meeting, American Association on Mental Retardation, Chicago. Contact M. Doreen Croser, Executive Director, 1719 Kalorama Road, NW, Washington, DC 20009; 202-387-1968.

May 29-June 3, 9th International Conference on Psychosomatic Obstetrics and Gynecology, Amsterdam. Contact Ms. G. van Notten, OBA, Europaplein 8, 1078 GZ, Amsterdam, Netherlands.

May 31-June 2, World Psychiatric Association Section of Epidemiology and Community Psychiatry, Toronto. Contact M.R. Eastwood, M.D., Clarke Institute of Psychiatry, 250 College Street, Toronto, Canada M5T 1R8; 416-979-6852 or 979-6841.

JUNE

June 1-3, 8th Society for Menstrual Cycle Research Conference, Salt Lake City. Contact Ann Voda, University of Utah, 25 South Medical Drive, Salt Lake City, UT 84112; 801-581-8272.

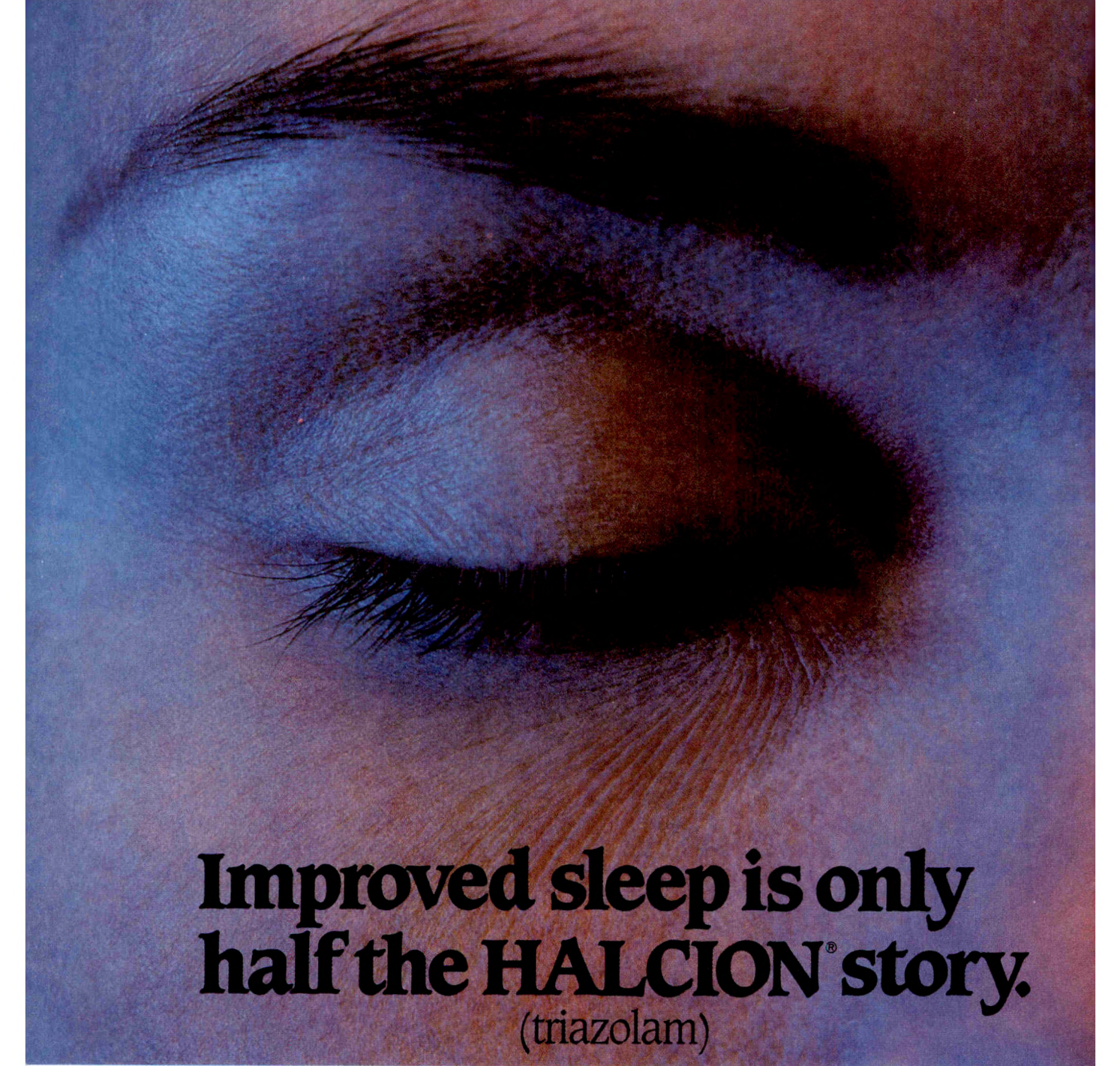
June 12-13, "Mental Health Services for Children and Adolescents in Primary Care Settings: A Research Conference," Hartford, Connecticut. Contact Phil Leaf, Ph.D., Yale Psychiatric Institute, 350 Congress Avenue, New Haven, CT 06519; 203-785-5551.

June 14-16, 12th Annual Convention of the International Psychohistorical Association, New York. Contact Professor Samuel S. Janus, Ph.D., Chair, Program Committee, P.O. 2247, Charlottesville, VA 22902; 804-971-8086.

June 15-16, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Minneapolis. Contact John Racy, M.D., 1501 North Campbell Avenue, Tucson, AZ 85724; 602-626-6512.

June 15-18, annual meeting, American Association of Neuropathologists, Dallas. Contact Reid R. Heffner, Jr., M.D., Executive Director, 462 Grider Street, Buffalo, NY 14215; 716-898-3117.

June 18-21, 16th Annual Conference, National Council for International Health, "Toward a Healthier World: Influencing International Policies and Strategies," Arlington, Virginia. Contact Conference Department, National Council for International Health, 1701 K Street, N.W., Suite 600, Washington, DC 20006.




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Effective, concomitant therapy.

HALCION was compared with placebo in a double-blind comparative study of 53 depressed outpatients who had been stabilized on a TCA for at least six weeks but who still suffered refractory insomnia. HALCION was shown to be more effective in relieving the symptoms of insomnia without making depressive symptoms worse.¹

A large, close-up photograph of a human eye, showing the iris, pupil, and eyelashes. The eye is looking directly at the viewer. The skin around the eye is visible, showing fine lines and texture.

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Daytime alertness is the other half.

In another double-blind study comparing HALCION with placebo in 78 depressed outpatients receiving 50-300 mg of imipramine per day, HALCION was significantly more effective in improving most sleep parameters. In addition, there was no evidence that HALCION interfered with the efficacy of imipramine or aggravated the patients' depressive symptoms.²

These studies suggest that HALCION is effective adjunctive therapy for the relief of short-term insomnia in depressed patients.

Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

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INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizzaro or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period.

Nursing Mothers: Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnesic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

B-5-S

References:

1. Cohn JB: Triazolam: treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
2. Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):656-665.

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Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients should include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

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Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

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These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

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The only difference between these two types of papers is length. **Regular Articles** contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. **Brief Communications** contain no more than 2,500 words, including an abstract of no more than 100 words, references, tables, and figures. (A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words.) Articles that exceed 3,800 words will be returned unreviewed to the authors.

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A prompt publication policy (i.e., publication within 4 to 6 months after acceptance) is in effect for Clinical and Research Reports. Manuscripts may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, text, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

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3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in *Endorphins in Mental Health Research*. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

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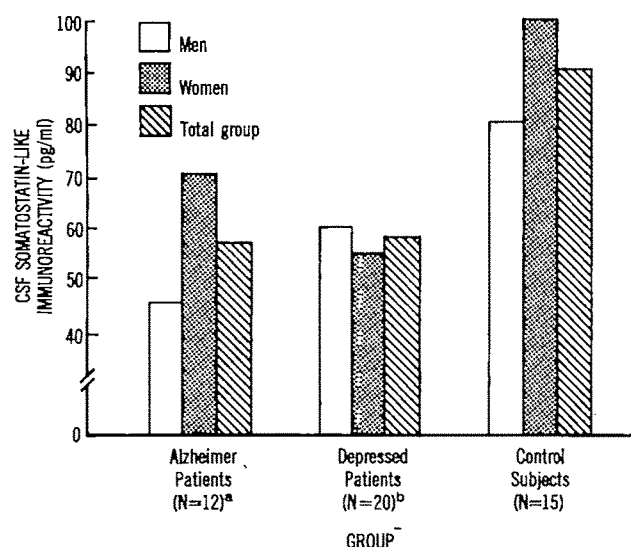
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FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



^aSignificant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

^bSignificant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

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Differentiating Anxiety and Depression

Gary Tollason, M.D.

Anxiety and Physical Illness

Charles K. Billings, M.D.

Use and Misuse of the Benzodiazepines in the Elderly

Earl A. Burch, M.D.

Diagnosis and Management of Panic Disorders

William G. Wood, M.D.

Panic Disorders: Psychotherapy, Psychopharmacology, Medical Psychiatry

David Harnett, M.D.

Eating Disorders

Medical Complications and Medical Management of Eating Disorders

James Mitchell, M.D.

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Kathi Sanderlin

Overview of Research on the Treatment of Bulimia Nervosa

James Mitchell, M.D.

Tuesday, March 21 Distinguished Professor Lectures

Paranoid Conditions Seen in Psychiatric Medicine

William Webb, M.D.

Importance of Treating Anxiety in the Elderly III Patient

Robert O. Pasnau, M.D.

The Consequences of Anxiety

Russell Noyes, M.D.

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New Advances in Psychotherapeutic Agents: Clozapine

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Clinical Psychopharmacology: Update

Thomas P. Beresford, M.D.

Med/Psych

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Richard C.W. Hall, M.D.

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Thomas N. Wise, M.D.

Functional Visual Loss as a Model for Pseudopsychiatry

Roger Kathol, M.D.

Wednesday, March 22 General Psychiatry

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Thomas N. Wise, M.D.

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Daniel K. Winstead, M.D.

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J. Raymond DePaulo, M.D.

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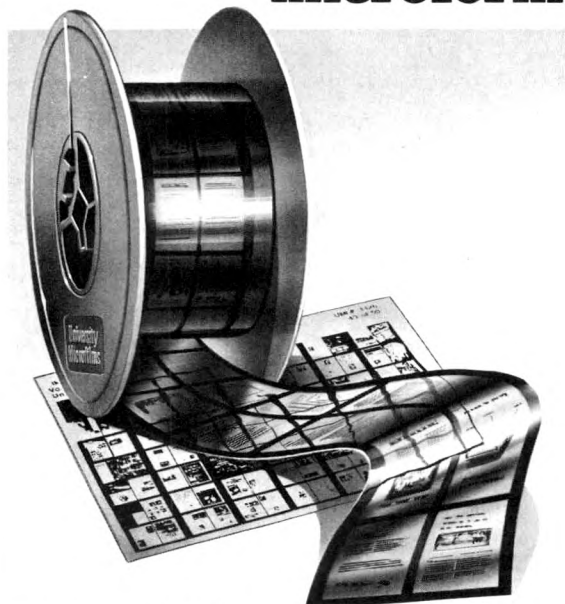
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HALDOL DECANOATE (HALOPERIDOL) INJECTION

**Sustained protection
for the schizophrenic patient
with a single monthly dose**

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsome activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. Tardive Dystonia—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.**

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

NOW AVAILABLE!
THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
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For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE (HALOPERIDOL) INJECTION

**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 3 March 1989

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By Brian F. Hoffman and Harvey Spiegel

Pathophysiology of HPA Axis Abnormalities
in Patients With Major Depression: An Update

By Roger G. Kathol, Richard S. Jaekle, Juan F. Lopez, et al.

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Physicians prescribe Ativan for what it doesn't do—as well as for what it does



Only Ativan offers all these benefits...

rapid relief of anxiety

clearance not significantly
delayed by age, liver or kidney
dysfunction

cumulative sedative effects
seldom a problem (Sedation, reported
in 15.9% of patients in clinical trials,
was generally mild and transitory.)

little likelihood of drug interaction
(All benzodiazepines produce additive
sedative effects when taken with
alcohol or other CNS depressants.)

no significant changes in vital
signs in cardiovascular patients*

short duration of action, simple
metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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(lorazepam) ^{IV}

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your patients' therapy

Indicate one of the following on your prescriptions, as
appropriate to your state laws:

- Do not substitute
- Dispense as written
- Medically necessary
- Brand necessary
- May not substitute
- No substitution
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levaterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.



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1

Ativan® doesn't
significantly delay clearance
because of age or kidney or
liver dysfunction

2

Ativan® doesn't
have any reported interactions
with numerous commonly
prescribed medications
(All benzodiazepines produce
additive sedative effects when
taken with alcohol or other
CNS depressants.)

3

Ativan® doesn't
have a complex
metabolism—has short duration
of action

5

Ativan® doesn't
cause significant changes in
vital signs in cardiovascular
patients*

4

Ativan® doesn't
have prolonged
accumulation—seldom
produces unwanted sedation
(Sedation, reported in 15.9%
of patients in clinical trials, was
generally mild and transitory.)

...it does effectively relieve anxiety

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Benzodiazepines have not been shown to be of benefit
in treating the cardiovascular component.

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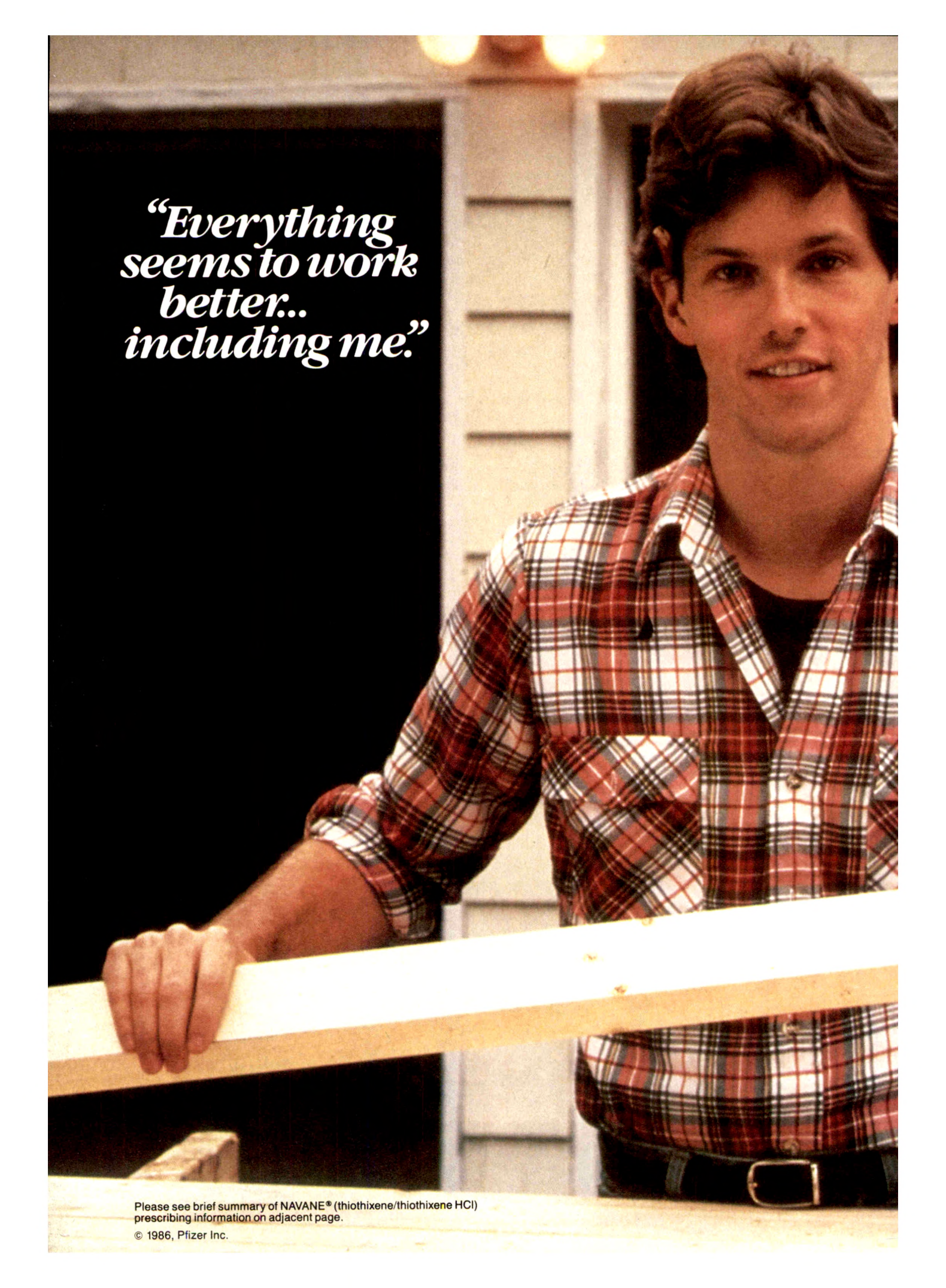
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A color photograph of a young man with dark, wavy hair, smiling slightly. He is wearing a red, white, and grey plaid button-down shirt over a dark t-shirt, and a dark belt with a silver buckle. He is leaning his right arm on a light-colored wooden railing. The background shows a white door with vertical panels and a dark interior. The lighting is warm, with a soft glow from a light source above.

*“Everything
seems to work
better..
including me.”*

Please see brief summary of NAVANE® (thiothixene/thiothixene HCl)
prescribing information on adjacent page.

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The background of the advertisement is a photograph of a person wearing a red and white plaid shirt, working on a large wooden frame structure in a workshop. The person's hands are visible, holding a piece of wood. The workshop is filled with various wooden beams and tools, creating a sense of active construction.

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For the chronic psychotic patient, Navane can mean improved motivation¹ and more competent work performance^{2,3}

Improvement generally occurs without serious side effects. Anticholinergic⁴ and cardiovascular^{5,6} side effects are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

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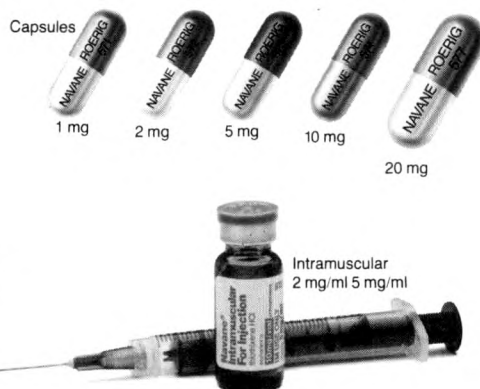
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References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Deming E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Deming E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoff RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Use in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Use in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenia [jaundice, biliary stasis] have been reported with related drugs).

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported with Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane injected well within the body of a relatively large muscle. The preferred sites are of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adult then only with caution to avoid radial nerve injury. Intramuscular injections of lower and mid-thirds of the upper arm. As with all intramuscular injections, avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic culture experiments indicate that approximately one third of human breast cancer *in vitro*, a factor of potential importance if the prescription of these drugs is for a previously detected breast cancer. Although disturbances such as galactorrhea, mastitis, and impotence have been reported, the clinical significance of elevated prolactin levels for most patients. An increase in mammary neoplasms has been found in administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies, however, have shown an association between chronic administration of these drugs and breast cancer; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed to chronic development tardive dyskinesia, it is advised that all patients in whom chronic use is possible, full information about this risk. The decision to inform patients and/or their families should take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic properties in common with the phenothiazines, all of the known side effects and toxicity associated with phenothiazines should be considered when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope occur, epinephrine should not be used as a pressor agent since a paradoxical pressure may result. Nonspecific EKG changes have been observed in some patients (thiothixene). These changes are usually reversible and frequently disappear on discontinuation of these changes is lower than that observed with some phenothiazines.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with Navane therapy. The incidence of sedation appears similar to that of the piperazine but less than that of certain aliphatic phenothiazines. Restlessness, agitation and hyperreflexia may occur. Seizures and paradoxical exacerbation of psychotic symptoms have been reported infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received Navane.

In addition, phenothiazine derivatives have been associated with cerebral edema and abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dyskinesia may require the use of an injectable antiparkinsonian agent. More slowly managed by reducing the dosage of Navane and/or administering an oral antiparkinsonian agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia on long-term therapy or may occur after drug therapy has been discontinued. It is characterized by rhythmic involuntary movements of the tongue, face, mouth, tongue, puffing of cheeks, puckering of mouth, chewing movements. Sometimes accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored. It has been reported that fine vermicular movement of the tongue may be an early sign of this or any other presentation of the syndrome is observed, the clinician should discontinue of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase have been infrequently observed in some patients. No clinically confirmed cases of Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leucopenia which are usually transient, can occur occasionally with Navane. Other antipsychotics associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with Navane. Undue exposure to sunlight should be avoided. Although Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have been reported in females receiving Navane. If persistent, this may necessitate a discontinuation of therapy. Phenothiazines have been associated with false pregnancy, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased salivation, and impotence have occurred infrequently with Navane. These have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, weight loss or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding information.

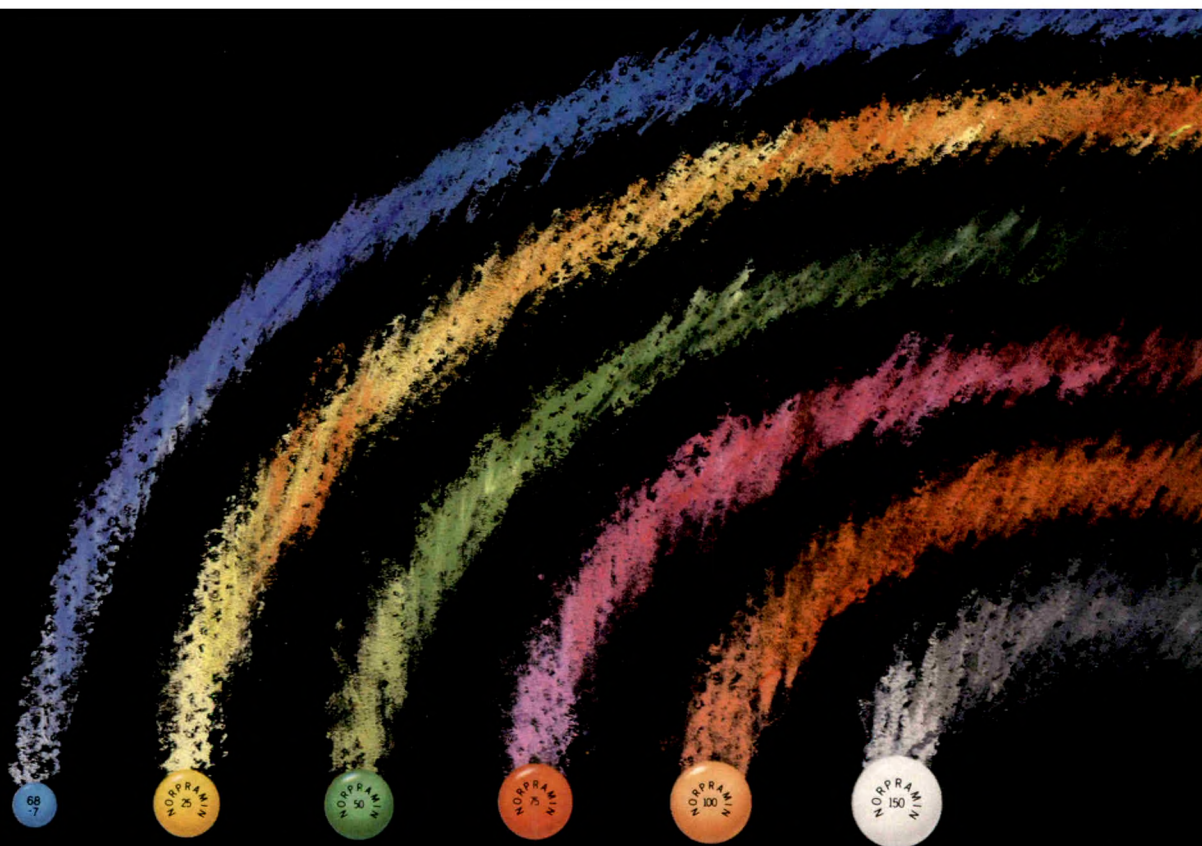
NOTE: Sudden deaths have occasionally been reported in patients who have received Navane. In some cases the cause of death was apparently cardiac arrest of the cough reflex. In others, the cause could not be determined nor could it be due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the clinical condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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(Brief Summary of Prescribing Information appears on the next page.)



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Norpramin (desipramine hydrochloride tablets USP)

*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

Merrell Dow U.S.A.

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Norpramin® 10, 25, 50, 75, 100, 150 mg (desipramine hydrochloride tablets USP)

Norpramin®

(desipramine hydrochloride tablets USP)

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

- Extreme caution should be used when this drug is given in the following situations:
 - In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
 - In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
 - In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
 - In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
- This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
- USE IN PREGNANCY**
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
- USE IN CHILDREN**
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
- The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS

- It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
- If serious adverse effects occur, dosage should be reduced or treatment should be altered.
- Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
- The drug may cause exacerbation of psychosis in schizophrenic patients.
- Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
- Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
- Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
- If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chloridazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
- Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
- This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
- Both elevation and lowering of blood sugar levels have been reported.
- Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure, constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling, elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here. Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

- Dialysis:** Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
- Pharmacologic treatment of shock:** Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.
- Pharmacologic control of seizures:** Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.
- Pharmacologic control of cardiac function:** Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

MERRELL DOW U.S.A.
A Division of Merrell Dow Pharmaceuticals Inc.
Cincinnati, Ohio 45215

Merrell Dow U.S.A.

The American Psychiatric Association

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Coming in the April 1989 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

Genetics and Psychiatry:

Past Discoveries, Current Dilemmas, and Future Directions
By Herbert Pardes, Charles A. Kaufmann, Harold Alan Pincus, et al.

Splitting in Hospital Treatment

By Glen O. Gabbard

Postcardiotomy Delirium: Conclusions After 25 Years?

By Lawrence W. Smith and Joel E. Dimsdale

CIBA-GEIGY ANNOUNCES



FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."¹ as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."²

A

treatment IND (investigational new drug)

program for

patients with

Obsessive-Compulsive Disorder

For information and enrollment kits call
1-800-842-2422
between 9AM-5PM Eastern Time

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

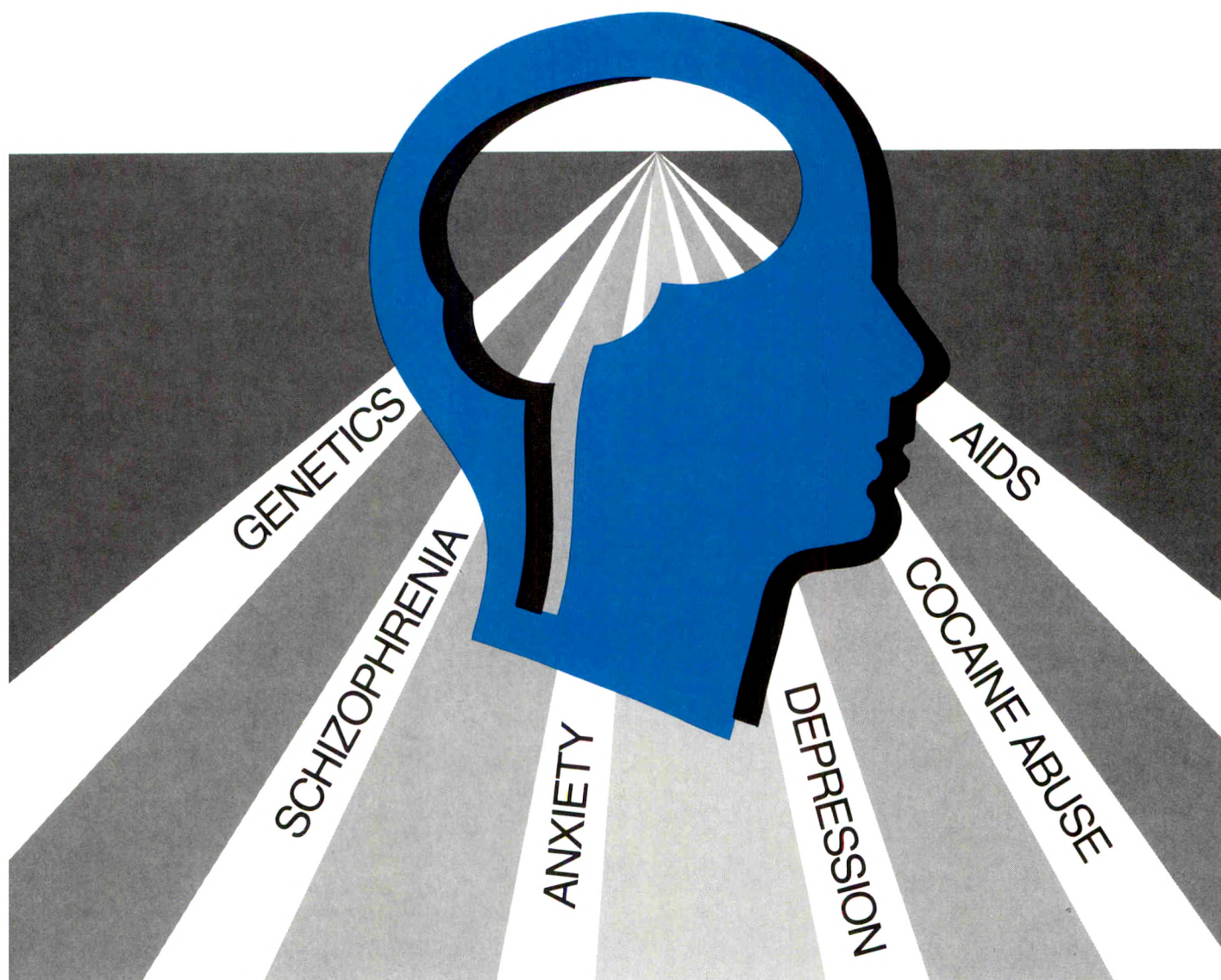
Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

¹ Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988;18:14-15.

²FDA Press Release, June 6, 1988.

NEW HORIZONS IN PSYCHIATRIC RESEARCH



Chairman:

Herbert Pardes, MD

New York Psychiatric Institute
Columbia University
College of Physicians and Surgeons
New York, New York

Psychiatric Aspects of AIDS

Frederick K. Goodwin, MD

Alcohol, Drug Abuse and Mental
Health Administration
Rockville, Maryland

**New Advances in Cocaine
Abuse Treatment**

Herbert D. Kleber, MD

Yale University School of Medicine
New Haven, Connecticut

**New Horizons for Depression
Associated with Medical Illness**

Charles Nemeroff, MD

Duke University Medical Center
Durham, North Carolina

**Schizophrenia: More Than
Medical Models**

Daniel R. Weinberger, MD

NIMH Neuroscience Center
Washington, DC

**New Horizons for Genetics and
Mental Illness**

Nancy Wexler, PhD

Columbia University
College of Physicians and Surgeons
New York, New York

**TUESDAY, MAY 9, 7:00 PM—10:00 PM
CONTINENTAL BALLROOMS 4, 5, 6
SAN FRANCISCO HILTON**

A buffet will be served at 5:30 p.m. before the symposium. After the program, there will be an opportunity to enjoy coffee and dessert with the speakers.

As an organization accredited by the ACCME to sponsor continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category 1 for the CME requirement of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.

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at the forefront of psychopharmacology

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THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

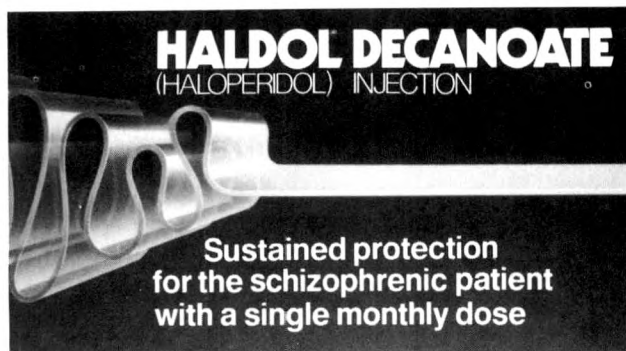
**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

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The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracocular pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thymotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinsonian drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. Tardive Dystonia—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.**

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdose, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

UPDATE ON NEW USES OF ANTIDEPRESSANTS

Tuesday, May 9, 1989
Ramada Renaissance Hotel
Renaissance Ballroom
San Francisco, California

Registration & Buffet, 6:00 pm - 7:00 pm
Scientific program, 7:00 pm - 10:00 pm

Chairman:

David J. Kupfer, MD
Professor and Chairman, University
of Pittsburgh School of Medicine
Western Psychiatric Institute and
Clinic, Pittsburgh, Pennsylvania

Psychopharmacologists have sought to both precisely define the uses of antidepressants as well as to broaden their indications for conditions that may not initially appear treatable by such agents. It is the purpose of this symposium to provide an update on these new uses for antidepressants, as well as to more precisely define the current range in which these therapeutic agents are indicated. It is expected that considerable information on the broader application of antidepressants—beyond their most conservative utilization—will be provided. In addition, the symposium faculty will offer objective guidelines for these new applications.

As an organization accredited by the ACCME to sponsor continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category I for the CME requirement of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.

Supported by an educational grant from
Merrell Dow Pharmaceuticals Inc.

Program and Faculty

Chairman's Introduction:
Survey of Research on New
Applications for Antidepressant
Agents

**Mechanisms of Action of
Anti-Panic Treatments**

Dennis S. Charney, MD
Associate Professor of Psychiatry
Yale University School of Medicine
New Haven, Connecticut

**Antidepressants in Treatment-
Refractory Patients**

Robert M. Post, MD
Chief, Biological Psychiatry Branch
National Institute of Mental Health
Bethesda, Maryland

**Antidepressants in the Treatment
of Chronic Pain**

Dietrich Blumer, MD
Professor and Director,
Neuropsychiatry Program
Department of Psychiatry
University of Tennessee
Memphis, Tennessee

**Antidepressant Use in
Eating Disorders**

David B. Herzog, MD
Associate Professor of Psychiatry
Director, Eating Disorders Unit
Massachusetts General Hospital
Boston, Massachusetts

**Antidepressants in Drug and
Alcohol Abuse Treatment**

Frank H. Gawin, MD
Assistant Professor of Psychiatry
Director, Stimulant Abuse
Treatment Program
Yale University School of Medicine
New Haven, Connecticut

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

MAY

May 1-5, annual meeting, American Pediatric Society, Washington. Contact Audrey Brown, M.D., Secretary-Treasurer, 450 Clarkson Avenue, Brooklyn, NY 11203; 718-270-1692.

May 3-7, annual meeting, American Psychoanalytic Association, San Francisco. Contact Helen Fischer, Administrative Director, 309 East 49th Street, New York, NY 10017; 212-752-0450.

May 3-7, annual meeting, Society of Biological Psychiatry, San Francisco. Contact David L. Dunner, M.D., Secretary-Treasurer, Harborview Medical Center ZA-15, Seattle, WA 98104; 206-223-3425.

May 4-7, annual meeting, American Association of Sex Educators, Counselors and Therapists, Washington. Contact Ruth Hunt, Ph.D., Executive Director, 11 Dupont Circle, NW, Suite 220, Washington, DC 20036; 202-462-1171.

May 4-7, annual meeting, American Academy of Psychoanalysis, San Francisco. Contact Vivian Mendelsohn, Executive Director, AAP, 30 East 40th Street, Room 206, New York, NY 10016; 212-679-4105.

May 5-7, annual meeting, American Society for Adolescent Psychiatry, San Francisco. Contact Mary D. Staples, Executive Secretary, 24 Green Valley Road, Wallingford, PA 19086; 215-566-1054.

May 6, annual meeting, American College of Psychoanalysts, San Francisco. Contact Harold Mann, M.D., Secretary General, 2006 Dwight Way #304, Berkeley, CA 94704; 415-845-7957.

May 6-7, annual meeting, American Association of Chairmen of Departments of Psychiatry, San Francisco. Contact Jeffrey L. Houpt, M.D., Secretary-Treasurer, Box AF, Emory University School of Medicine, Atlanta, GA 30322; 404-727-5881.

May 6-7, annual meeting, Black Psychiatrists of America, San Francisco. Contact Thelisa Harris, M.D., President, 664 Prospect Avenue, Hartford, CT 06105; 203-236-2320.

May 6-12, annual meeting, American Psychiatric Association, San Francisco. Contact Ms. Kathleen Bryan, Office of Meetings Management, American Psychiatric Association,

1400 K Street, N.W., Washington, DC 20005; 202-682-6076.

May 9-12, 6th International Meeting, International Study Group for Tryptophan Research, Baltimore. Contact Dr. Robert Schwarcz, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228; 301-455-7635

May 11-14, annual meeting, American Geriatrics Society, Boston. Contact Linda Hiddeman Barondess, Executive Vice-President, 770 Lexington Avenue, Suite 400, New York, NY 10021; 212-308-1414.

May 12, The Institute for Addiction Studies presents "Intervention: Clinical vs. Salesmanship," Oakland, California. Contact Stephanie Ross, MPI CDRH, 435 Hawthorne Avenue, Oakland, CA 94609; 415-428-4104

May 12-14, annual meeting, American Society of Group Psychotherapy and Psychodrama, New York. Contact Stephen F. Wilson, A.C.S.W., Executive Director, 116 East 27th Street, New York, NY 10016; 212-725-0046.

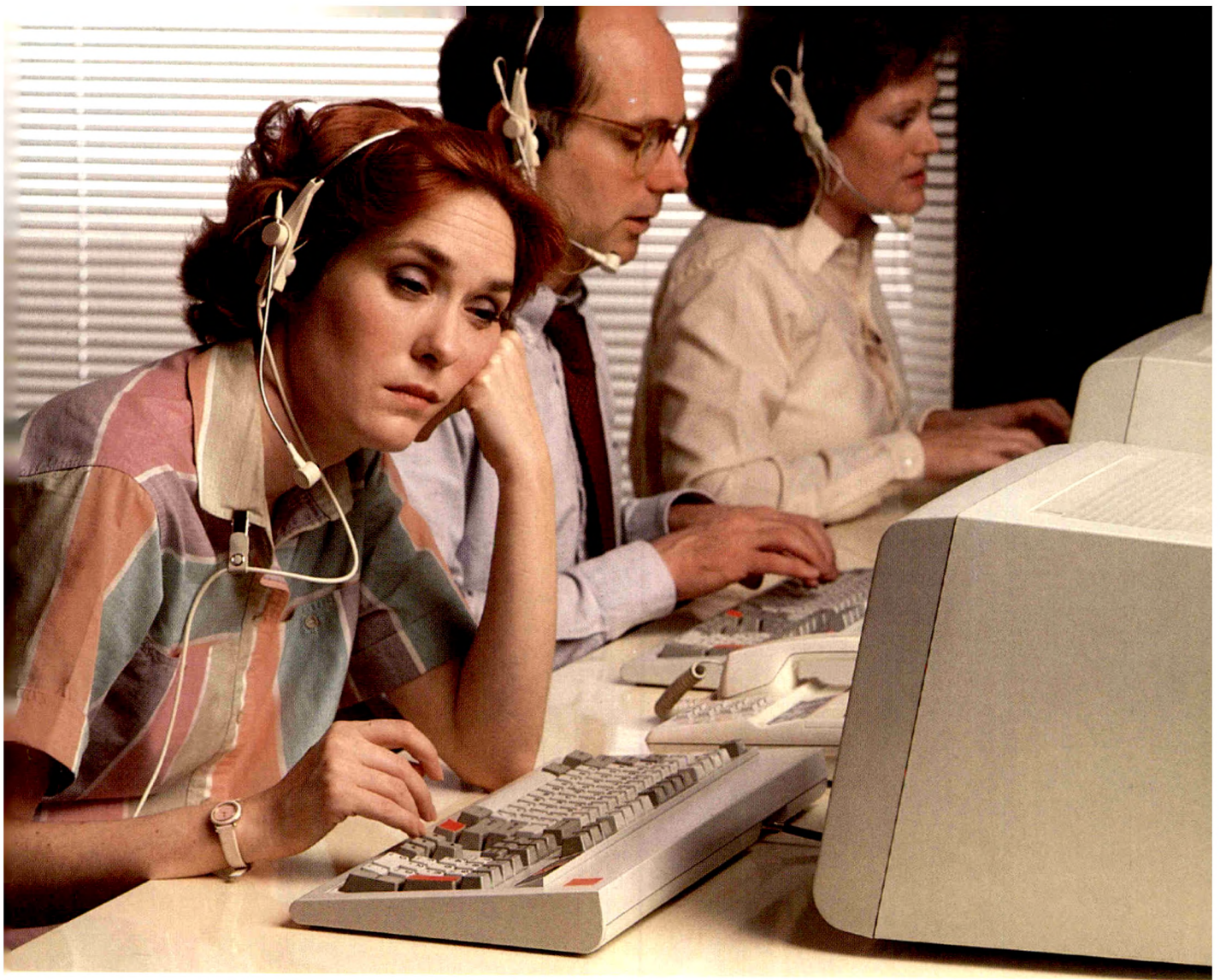
May 13-17, 24th Annual Meeting and Exposition of the Association for the Advancement of Medical Instrumentation, St. Louis. Contact Anna Belousovitch or Debbie Tritle, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598; 800-332-2264 or 703-525-4890.

May 14-19, 25th Annual Meeting Congress, The Royal Australian and New Zealand College of Psychiatrists, Honolulu. Contact Conference Associates, 335 Moray Street, South Melbourne 3205, Australia; 03-699-3955.

May 15, deadline for entries for The Manfred S. Guttmacher Award for outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work presented at a professional meeting or published between May 1, 1988 and April 30, 1989. Contact William H. Reid, M.D., M.P.H., Chairman, Guttmacher Award Board, American Psychiatric Association, 1400 K Street, N.W., Suite 327, Washington, DC 20005.

May 20, annual meeting, Recovery, Incorporated (The Association of Nervous and Former Mental Patients), Chicago. Contact Mary Jane Maggio, President, 802 North Dearborn Street, Chicago, IL 60610; 312-337-5661.

(Continued on page A34)



Asleep at the switch. This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation.
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When patients with depression are being treated with PAMELOR, they're able to keep operating on all circuits.

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What's more, PAMELOR has a low incidence of anticholinergic^{2,3,7} and hypotensive^{2,4,7-10} side effects. So, for those patients on another antidepressant, a switch to

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All the efficacy of amitriptyline¹ and

- little daytime sedation²⁻⁷
- low incidence of orthostatic hypotension^{2,4,7-10}
- low incidence of anticholinergic side effects^{2,3,7}

References: 1. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry*. May 1977;34:607-612. 2. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine*. August 1983;51:87-109. 3. Georgotas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive textbook of psychiatry IV*. Baltimore, Md: Williams & Wilkins, 1985:1821-833. 4. Blackwell B, Peterson GR, Kuzma RJ, Hosteller RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol*. 1980;4:255-261. 5. Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol*. 1978;6:155-161. 6. Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry*. 1982;17:535-546. 7. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm*. 1986;5:471-480. 8. Roose SP, Glassman AH, Siris SG, Walsh BT, Bruno RL, Wright LB. Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol*. 1981;1:316-319. 9. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed. New York, NY: Macmillan Publishing Co. 1985:413-423. 10. Thaysen P, Bjerre M, Kragh-Sorensen P, et al. Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology*. 1981;74:360-364.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor[®] (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor[®] (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time, myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such

as operating machinery or driving a car, therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC and lower clearance of nortriptyline.

Use in Pregnancy: Safe use during pregnancy and lactation has not been established, therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children: Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment. In this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: Cardiovascular: Hypotension, hypertension,

tachycardia, palpitation, myocardial infarction, arrhythmias, block, stroke. **Psychiatric:** Confusional states (especially in elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, panic, nightmares, hypomania, exacerbation of psychosis. **Neurologic:** Numbness, tingling, paresthesias, tremors, incoordination, ataxia, tremors, peripheral neuropathy, pyramidal symptoms, seizures, alteration in EEG patterns. **Anticholinergic:** Dry mouth and, rarely, associated sublingualitis; blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention, delayed micturition, dilation of the urinary tract. **Allergic:** Skin rash, petechiae, urticaria, itching, hypersensitivity (avoid excessive exposure to sunlight), edema (of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. **Hematologic:** Bone marrow depression, including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea and vomiting, anorexia, epigastric distress, diarrhea, paresthesia, stomatitis, abdominal cramps, black tongue. **Endocrine:** Gynecomastia in the male, breast enlargement and galactorrhea in female, increased or decreased libido, impotence, testicular swelling or depression of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Jaundice (simultaneous), altered liver function, weight gain or loss, perspiration, flushing, urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue, headache, parotid swelling, alopecia. **Withdrawal Symptom:** Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperreflexia, muscle rigidity, hyperactive tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM-217-1]



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Meeting Attendees**

**Sandoz Pharmaceuticals
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PHARMACOLOGIC THERAPY AND THE LONG-TERM COURSE OF SCHIZOPHRENIA

Sunday, May 7, 1989

San Francisco Hilton • Continental Ballroom
San Francisco, California

7:30 — 10:30 PM

A dinner buffet will be served at 9:45 PM following the symposium

Areas of discussion will include:

Overview of schizophrenia

Treatment options

Social functions of the treatment-resistant schizophrenic

Management of pharmacologic side effects

Psychological rehabilitation

Chairperson

Herbert Y. Meltzer, MD

Douglas Danford Bond Professor of Psychiatry
Case Western Reserve University
School of Medicine, Cleveland, Ohio

Speakers:

William T. Carpenter, Jr., MD
Director, Maryland
Psychiatric Research Center
and Professor of Psychiatry
University of Maryland
School of Medicine
Baltimore, Maryland

Dieter Naber, MD
Associate Professor of
Psychiatry
Department of Psychiatry
University of Munich
Munich, West Germany

John M. Kane, MD
Chairman, Department of
Psychiatry
Long Island Jewish
Medical Center
Professor of Psychiatry
School of Medicine, State
University of New York
Stony Brook, New York

Robert P. Liberman, MD
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Books Received

- Sensitivity—Agony or Ecstasy**, by G. Burton Appleford, M.D., F.A.P.A. Bryn Mawr, Pa., Dorrance & Co., 1988, 63 pp., \$7.95 (paper).
- One Foot in Eden: A Sociological Study of the Range of Therapeutic Community Practice**, by Michael Bloor, Neil McKeganey, and Dick Fonkert. New York, Routledge, 1988, 239 pp., \$55.00.
- Helping Women Keep Well: A Guide to Health Promotion and Illness Prevention for the Health Professional**, by Richard H. Blum, Ph.D., and W. Leroy Heinrichs, M.D., Ph.D. New York, Irvington, 1988, 425 pp., \$49.95.
- Anxiety and Depressive Disorders in the Medical Patient**, by Leonard R. Derogatis, Ph.D., and Thomas N. Wise, M.D. Washington, D.C., American Psychiatric Press, 1989, 260 pp., \$21.95.
- Family Violence: Emerging Issues of a National Crisis**, edited by Leah J. Dickstein, M.D., and Carol C. Nadelson, M.D. Washington, D.C., American Psychiatric Press, 1989, 266 pp., \$21.95.
- One to One: The Experience of Psychotherapy**, by Rosemary Din-nage. New York, Viking, 1988, 219 pp., \$17.95.
- Working With People: Clinical Uses of Personal Construct Psychology**, edited by Gavin Dunnett. New York, Routledge, 1988, 212 pp., \$49.50; \$14.95 (paper).
- Race and Culture in Psychiatry**, by Suman Fernando. London, Croom Helm (New York, Routledge, Chapman & Hall, distributor), 1988, 204 pp., \$49.95.
- Selective 5-HT Reuptake Inhibitors: Novel or Commonplace Agents?** edited by M. Gastpar and J.S. Wakelin. Basel, Karger, 1988, 103 pp., \$65.50.
- Differing Approaches to Partial Hospitalization: New Directions for Mental Health Services**, number 38, summer 1988, edited by Kenneth Goldberg. San Francisco, Jossey-Bass, 1988, 97 pp., \$12.95 (paper).
- Drug Interactions: Clinical Significance of Drug-Drug Interactions**, 6th ed., by Philip D. Hansten, Pharm.D., and John R. Horn, Pharm.D. Philadelphia, Lea & Febiger, 1989, 428 pp., \$65.00 (loose-leaf notebook).
- Communicating With Patients: Improving Communication, Satisfaction and Compliance**, by Philip Ley. New York, Croom Helm (Routledge, Chapman & Hall, distributor), 1988, 206 pp., \$49.95; \$17.95 (paper).
- Schizophrenia: Treatment Process and Outcome**, by Thomas H. McGlashan, M.D., and Christopher J. Keats, M.D. Washington, D.C., American Psychiatric Press, 1989, 195 pp., \$28.00.
- Innovations in Health Care Practice**, edited by John S. McNeil and Stanley E. Weinstein. Silver Spring, Md., National Association of Social Workers, 1988, 136 pp., \$12.95 (paper).
- The Nervous System**, 3rd ed., by Peter Nathan, M.D., F.R.C.P. New York, Oxford University Press, 1988, 371 pp., \$14.95 (paper).
- The Boy Who Couldn't Stop Washing: The Experience and Treatment of Obsessive-Compulsive Disorder**, by Judith L. Rapoport, M.D. New York, E.P. Dutton, 1989, 248 pp., \$18.95.
- Killer Sleep: Uncovering a Hidden Disease**, by David Leigh Rodgers, M.D. San Francisco, David Leigh Rodgers, M.D., 1988, 201 pp., \$6.95 (paper).
- Research to Practice in Community Psychiatry**, edited by M.A.J. Romme, M.D., Ph.D., M.R.C.Psych.; A.D.M.A.C. Escher, technical editor. Assen, The Netherlands, Van Gorcum, 1988, 92 pp., 24,00 Dfl (paper).
- Child Psychopathology and the Quest for Control: Developmental Clinical Psychology and Psychiatry**, vol. 17, by Fred Rothbaum and John R. Weisz. Newbury Park, Calif., Sage Publications, 1989, 130 pp., \$19.95; \$12.95 (paper).
- Anxiety: New Findings for the Clinician**, edited by Peter P. Roy-Byrne, M.D. Washington, D.C., American Psychiatric Press, 1989, 204 pp., \$19.95.
- Lithium Treatment of Manic-Depressive Illness: A Practical Guide**, 4th ed., by Mogens Schou. Basel, Karger, 1989, 46 pp., no price listed (paper).
- Occupational Therapy in Mental Health: Principles in Practice**, edited by Derek W. Scott and Noomi Katz. New York, Taylor & Francis, 1988, 220 pp., \$33.00 (paper).
- Serving the Chronically Mentally Ill in an Urban Setting: The Massachusetts Mental Health Center Experience. New Directions for Mental Health Services**, number 39, fall 1988, edited by Miles F. Shore and Jon E. Gudeman. San Francisco, Jossey-Bass, 1988, 102 pp., \$14.95 (paper).
- DSM-III-R Casebook: A Learning Companion to the Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised)**, by Robert L. Spitzer, M.D., Miriam Gibbon, M.S.W., Andrew E. Skodol, M.D., Janet B.W. Williams, D.S.W., and Michael B. First, M.D. Washington, D.C., American Psychiatric Press, 1989, 515 pp., \$37.50.
- Churchill's Black Dog, Kafka's Mice, and Other Phenomena of the Human Mind**, by Anthony Storr. New York, Grove Press, 1988, 310 pp., \$19.95.
- Weight, Sex and Marriage: A Delicate Balance** (1987), by Richard B. Stuart and Barbara Jacobson. New York, Fireside Books (Simon & Schuster), 1989, 182 pp., \$6.95 (paper).
- The Perspective of John Talbott: New Directions for Mental Health Services**, number 37, spring 1988, by John A. Talbott. San Francisco, Jossey-Bass, 1988, 107 pp., \$12.95 (paper).
- Computer Psychology Systems: Theory and Research Foundations**, by Morton Wagman. New York, Gordon and Breach Science Publishers (Harwood Academic Publishers), 1988, 247 pp., \$68.00.
- Menschen einer Psychiatrie: Wie normal sind die Normalen?** by Bernhard Wagner. Constance, West Germany, Verlag Rainer Magulski, 1988, 192 pp., no price listed (paper).
- Eating Behavior in Eating Disorders**, edited by B. Timothy Walsh, M.D. Washington, D.C., American Psychiatric Press, 1988, 232 pp., \$22.95.
- In a Darkness: The Story of a Young Suicide**, 2nd ed., by James A. Wechsler with Holly W. Schwartz, Ph.D., and Nancy F. Wechsler. Miami, Pickering Press, 1988, 208 pp., \$12.95 (paper).
- Aspects of Autism: Biological Research**, edited by Lorna Wing. London, Gaskell (Royal College of Psychiatrists)/National Autistic Society, 1988, 114 pp., £7.50 (paper).
- Tardive Dyskinesia: Biological Mechanisms and Clinical Aspects**, edited by Marion E. Wolf, M.D., and Aron D. Mosnaim, Ph.D. Washington, D.C., American Psychiatric Press, 1988, 290 pp., \$29.95.

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Professor and Director
Adult Psychiatry Clinical Services
Department of Psychiatry &
Biobehavioral Sciences
UCLA School of Medicine
Los Angeles, California
Past President, American
Psychiatric Association

The Silent Partner

Sunday, May 7, 1989 Anxiety and AIDS

Opening Comments
Paul Jay Fink, MD
Chairman, Department of Psychiatry
Albert Einstein Medical Center
Philadelphia, Pennsylvania
Medical Director,
Philadelphia Psychiatric Center
President, American
Psychiatric Association

Anxiety and Stigmatizing Aspects of HIV Infection
Mindy Fullilove, MD
Assistant Clinical Professor of
Psychiatry and Epidemiology
UCSF School of Medicine
San Francisco, California

Anxiety and the Neuropsychiatry of AIDS
Francisco Fernandez, MD
Chief, Psychiatric
Consultation Service
St. Luke's Episcopal Hospital
Assistant Professor of Psychiatry
Baylor College of Medicine
Houston, Texas

Monday, May 8, 1989 Anxiety and The Family

Opening Comments
John A. Talbott, MD
Professor and Chairman
Department of Psychiatry
University of Maryland
School of Medicine
Baltimore, Maryland
Past President, American
Psychiatric Association

Family Anxiety and Victims of Traumatic Events
Lenore Cagen Terr, MD
Clinical Professor of Psychiatry
UCSF-Langley Porter
Neuropsychiatric Institute
San Francisco, California

Family Anxiety and Parental Cancer
Jimmie Holland, MD
Professor of Psychiatry
Cornell University Medical College
Chief, Psychiatry Service
Memorial Sloan Kettering
Cancer Center
New York, New York

Tuesday, May 9, 1989 Anxiety and Substance Abuse

Opening Comments
Daniel X. Freedman, MD
Judson Braun Professor of
Psychiatry and Pharmacology
Director, Division of
Adult Psychiatry
UCLA School of Medicine
Los Angeles, California
Past President, American
Psychiatric Association

Anxiety and Drug Abuse
Professor Sir Martin Roth, MD, ScD, FRC Psych
Fellow of Trinity College
University of Cambridge
Cambridge, England

Anxiety and Alcoholism
V. Markku I. Linnoila, MD, PhD
Clinical Director
Division of Intramural Clinical and
Biological Research
National Institute on Alcohol Abuse
and Alcoholism
Alcohol, Drug Abuse and Mental
Health Administration
Bethesda, Maryland

Wednesday, May 10, 1989 Anxiety and Physical Illness

Opening Comments
Louis Jolyon West, MD
Professor and Chairman
Department of Psychiatry and
Biobehavioral Sciences
Director, Neuropsychiatric Institute
UCLA School of Medicine
Los Angeles, California

Anxiety and Coronary Heart Disease in Midlife
Richard H. Rahe, MD
Professor of Psychiatry
Department of Psychiatry and
Behavioral Sciences
University of Nevada
School of Medicine
Reno, Nevada

Anxiety and Physical Illness in the Elderly
James Turnbull, MD, FRCP (C)
Professor and Chairman
Department of Psychiatry and
Behavioral Sciences
Quillen-Dishner
College of Medicine
East Tennessee State University
Johnson City, Tennessee

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Chief, Clinical Psychopharmacology
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Massachusetts General Hospital
Boston, Massachusetts

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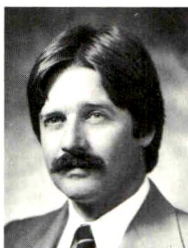
Elliot S. Gershon, MD
Chief, Clinical Neurogenetics Branch
National Institute of Mental Health
Bethesda, Maryland

***The New Outlook on Genetics and
Environment in Bipolar Affective
Disorder***



Thomas A. Wehr, MD
Chief, Clinical Psychobiology Branch
National Institute of Mental Health
Intramural Research Program
Bethesda, Maryland

***Sleep Disruption and
Environmental Precipitants***



Frederick K. Goodwin, MD
Administrator, Alcohol, Drug Abuse and
Mental Health Administration
Rockville, Maryland

***The Biology of Recurrence: New
Directions for the Pharmacological
Bridge***



Alan J. Gelenberg, MD
Associate Professor of Psychiatry
Harvard Medical School, and
Chief, Special Studies Clinic
Massachusetts General Hospital, and
Psychiatrist-in-Chief, The Arbour
Boston, Massachusetts

***Maintenance Lithium Levels:
New Findings***



Robert M. Post, MD
Chief, Biological Psychiatry Branch
National Institute of Mental Health
Intramural Research Program
Bethesda, Maryland

***Kindling Models and
Anticonvulsants in Mania***



Gary S. Sachs, MD
Instructor in Psychiatry
Harvard Medical School, and
Director, Chronobiology Section
Clinical Psychopharmacology Unit
Massachusetts General Hospital
Boston, Massachusetts

***Adjuncts and Alternatives to
Lithium Therapy***

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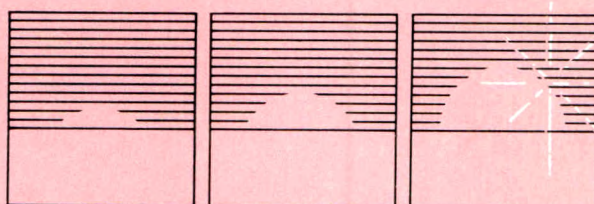
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PERSPECTIVES



New Modalities For Managing Depression

Chairman, William Z. Potter, MD, PhD • National Institute of Mental Health

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“Experimental Approaches to the Treatment of Depression”

■ **John Feighner, MD**
Feighner Research Institute
“Bupropion: A New Pharmacologic Modality”

■ **William Z. Potter, MD, PhD**
National Institute of Mental Health
“New Clinical Approaches to the Treatment of Depression”

■ **A. John Rush, MD**
University of Texas Health Sciences Center
“Promising Psychotherapeutic Treatments for Depression”

■ **Gary Tollefson, MD, PhD**
St. Paul-Ramsey Medical Center
“Assimilation of New Modalities into Clinical Practice”


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9:00 AM to 12:00 NOON
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INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	897
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnesic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

B-6-S

References:

- Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
- Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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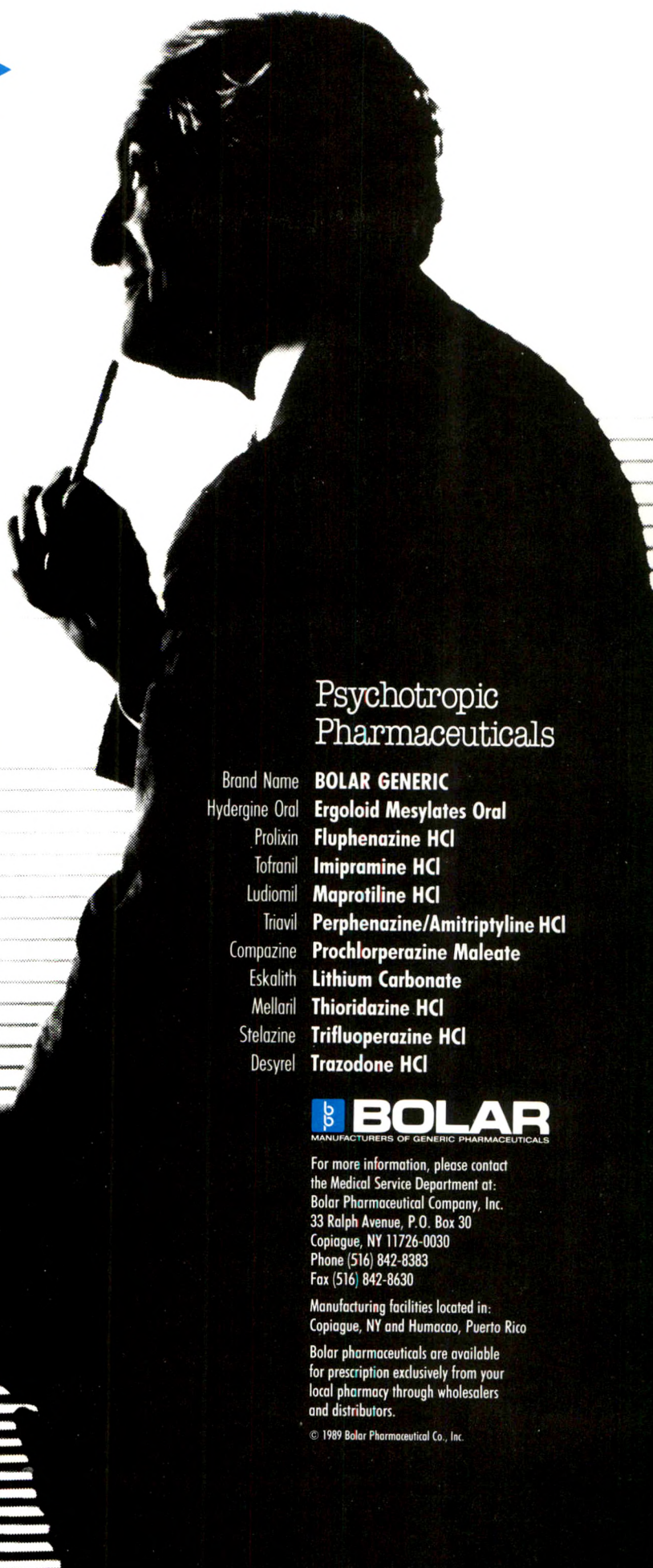
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(Continued from page A18)

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May 23–25, 35th Annual Meeting of the American Society for Artificial Internal Organs, Dallas. Contact ASAO Annual Meeting, P.O. Box C, Boca Raton, FL 33429; 407-391-8589.

May 28–31, annual meeting, Association for the Care of Children's Health, Anaheim, California. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, 3615 Wisconsin Avenue, N.W., Washington, DC 20016.

May 28–June 1, annual meeting, American Association on Mental Retardation, Chicago. Contact M. Doreen Croser, Executive Director, 1719 Kalorama Road, NW, Washington, DC 20009; 202-387-1968.

May 29–June 3, 9th International Conference on Psychosomatic Obstetrics and Gynecology, Amsterdam. Contact Ms. G. van Notten, OBA, Europaplein 8, 1078 GZ, Amsterdam, Netherlands.

May 31–June 2, World Psychiatric Association Section of Epidemiology and Community Psychiatry, Toronto. Contact M.R. Eastwood, M.D., Clarke Institute of Psychiatry, 250 College Street, Toronto, Canada M5T 1R8; 416-979-6852 or 979-6841.

JUNE

June 1, The Institute for Addiction Studies presents "Adult Children of Alcoholics: Theory & Practice," Oakland, California. Contact Stephanie Ross, MPI CDRH, 435 Hawthorne Avenue, Oakland, CA 94609; 415-428-4104.

June 1–3, 8th Society for Menstrual Cycle Research Conference, Salt Lake City. Contact Ann Voda, University of Utah, 25 South Medical Drive, Salt Lake City, UT 84112; 801-581-8272.

June 9–11, Part II Examinations, American Board of Psychiatry and Neurology, Denver. Contact Stephen C. Scheiber, M.D., Executive Secretary, 500 Lake Cook Road, Suite 335, Deerfield, Illinois 60015.

June 12–13, "Mental Health Services for Children and Adolescents in Primary Care Settings: A Research Conference," Hartford, Connecticut. Contact Phil Leaf, Ph.D., Yale Psy-

chiatric Institute, 350 Congress Avenue, New Haven, CT 06519; 203-785-5551.

June 14–16, 12th Annual Convention of the International Psychohistorical Association, New York. Contact Professor Samuel S. Janus, Ph.D., Chair, Program Committee, P.O. 2247, Charlottesville, VA 22902; 804-971-8086.

June 15–16, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Minneapolis. Contact John Racy, M.D., 1501 North Campbell Avenue, Tucson, AZ 85724; 602-626-6512.

June 15–18, annual meeting, American Association of Neuropathologists, Dallas. Contact Reid R. Heffner, Jr., M.D., Executive Director, 462 Grider Street, Buffalo, NY 14215; 716-898-3117.

June 18–21, 16th Annual Conference, National Council for International Health, "Toward a Healthier World: Influencing International Policies and Strategies," Arlington, Virginia. Contact Conference Department, National Council for International Health, 1701 K Street, N.W., Suite 600, Washington, DC 20006.

June 18–22, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn Street, Chicago, IL 60610; 312-645-5000.

June 19–21, annual meeting, Committee on Problems of Drug Dependence, Inc., Keystone, Colorado. Contact Martin W. Adler, Ph.D., Executive Secretary, 3420 North Broad Street, Philadelphia, PA 19140; 215-221-3298.

June 21–24, International Symposium on Alzheimer's Disease, Wurzburg, West Germany. Contact Department of Psychiatry, Fuchsleinstr. 14, D-8700 Wurzburg, Federal Republic of Germany.

June 21–24, 7th International Symposium on "Adapted Physical Activity—An Interdisciplinary Approach," Berlin. Contact 7th ISAPA Berlin '89, Institut fur Sportwissenschaft, Rheinbabenalle 14, D-1000 Berlin 33, West Germany; 030-824-3731.

June 24–27, annual meeting, American Nurses' Association, Kansas City, Missouri. Contact Judith A. Ryan, Ph.D., R.N., Executive Director, 2420 Pershing Road, Kansas City, MO 64108; 816-474-5720.

June 25–30, 15th International Congress on Law and Mental Health, Jerusalem. Contact Congress Organizers International, Ltd., P.O. Box 29313, 65121 Tel Aviv, Israel.

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The 1948 United Nations Universal Declaration of Human Rights recognized "the inherent dignity and . . . the equal and inalienable rights of all members of the human family" as including a right of "free and full development of . . . personality" within a person's community, noting the importance of equal rights for men and women and a positive right to education (1). Freedom from medical treatment without informed consent, a share in the benefits of scientific advancement, and the highest obtainable standards of physical and mental health were also regarded as human rights.

It was not until 20 years later that the 1968 International Conference on Human Rights warned that "recent scientific discoveries and technological advances . . . may . . . endanger the rights and freedoms of individuals and will require continuing attention" (2).

By this time American psychiatry, as well as psychology, social work, and consumer groups, had become concerned with the possible impairment of personal autonomy by the behavior therapies, neuroleptic drugs, ECT, and the psychosurgeries. APA also turned its attention to the mental health aspects of nonpsychiatric technologies, establishing in 1971 a task force on psychiatric involvement in family planning (3). That task force devoted special attention to the psychosocial issues inherent in the prescription, use, and prohibition of proceptive and contraceptive technologies, including pregnancy termination. However, its purview appeared too politically sensitive and it was terminated after 2 years. Another 16 years elapsed before APA directed official attention to the arena of reproductive technology with its establishment in 1987 of a committee on women. Meanwhile, the 1985 Nairobi conference, concluding the United Nations Decade for Women, had declared that "the ability of women to control their own fertility" is "an important basis for the enjoyment of other rights" (4). Shortly thereafter the Division of Human Rights and Peace of the United Nations Educational, Scientific, and Cultural Organization (UNESCO) stated that advances in biomedical science and technology must "decrease the economic and cultural disparities among social and national groups" (5). Subsequently UNESCO, through the International Social Science Council, commissioned working groups, through contract with the World Federation for Mental Health, on the impact of the new reproductive technologies on women's rights and the impact of advancing biomedical technology on human rights in general.

The draft reports of both groups (6, 7) emphasize the role of physicians as protectors of the rights of patients and families, recognizing that social policy and technological advances in medicine are always mediated for the individual patient through his or her interaction with a physician. Except for euthanasia, relatively little attention has focused on whether or not a physician should be regarded solely as a technician in pursuit of the patient's or the family's desire, within the constraints of social policy, or whether she or he should be held ethically as well as clinically responsible for the procedures' outcome. Almost no one has asked if the physician can ethically consider these issues without specific and informed attention to the psychological well-being of all concerned. The importance of the problem is underscored by the accelerating flow of high-technology medical devices contributing to the development of a medical subculture that values technology perceived as a mark

of "objectivity" (8). Under these circumstances unrecognized, and perhaps unjustified, therapeutic ambition can contribute to the belief that all available technologies should be used—not only to ameliorate disorder or postpone death, but to gratify desire. As in the case of women with a "desperate" desire for a child, who seek fulfillment through in vitro fertilization, this can make it almost impossible to counsel patients about where their "best interest" really lies (9).

In our modern industrial society the increasingly frequent demands on the feelings, values, and beliefs of doctors, patients, and relatives, in regard to decisions formerly made by nature or involving previously inconceivable possibilities, require attention to the cornerstones of ethical practice: the principles of autonomy, beneficence, and justice. Autonomy means preserving the patient's freedom of choice and capacity for self-determination. Beneficence means making clinical decisions in terms of the best interest of the patient, not that of family, community, state, or physician. Justice means preserving equity of access to necessary diagnosis and treatment, as well as equity regarding coercion, restraint, or compulsory treatment.

In the pressure cooker of medical decision making the abstract advice of ethicists may be unavailable or perceived as irrelevant. The patient's best interest may be ignored in favor of his or her expressed desire, which the doctor takes at face value, and in favor of the doctor's own automatic conformity to the technological subculture of medicine. Many physicians regard the availability of new technology as carrying a moral imperative for its use. This impairs their ability to identify and frame the relevant ethical questions in a case (9). In addition, and understandably, the wish to give their patients the benefit of the new procedures is reinforced by the excitement the new technology gives to their practices. Doctors have repeatedly been demonstrated to be advocates of the particular technologies in which they themselves are expert and to which they attach high value (10). Most do not have the time, interest, or training to work psychotherapeutically with patients (or relatives) to help them discover what they really want (which may not be the new procedure) and what is in their best interest, so that they may make their own best decisions. Most have little perception of the possible countertransference factors or the unconscious culture-bound moral judgments that may influence their work with their patients.

Under these circumstances consultation can be vital. The nonpsychiatric physician's natural ally is the psychiatrist. In order to be an effective consultant the psychiatrist must understand the impact of society and culture, as well as past personal history and individual psychology, on feelings, beliefs, and values. More specifically, he or she must be knowledgeable about the concept of human rights, the impact of the emerging biomedical technologies on them, tools for ethical analysis, and comparative values as determinants of medical and personal decision making. A curriculum essential for accomplishing this difficult assignment is still to be developed. It should include elements of the law, ethics, social structure (sociology), and comparative values (anthropology). Together with the psychiatrist's basic professional skills, a firm understanding of contemporary biomedicine and its technologies, and the capacity for dialogue with fellow physicians in all specialties, this knowledge can fit the liaison psychiatrist for the new and exciting challenges in medical care that are coming, increasingly, to dominate our era.

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EUGENE B. BRODY, M.D.

Dr. Brody is Secretary General, World Federation for Mental Health. Address reprint requests to Dr. Brody, The Sheppard and Enoch Pratt Hospital, P.O. Box 6815, Baltimore, MD 21285-6815.

The Meaning of Culturally Sensitive Research in Mental Health

Lloyd H. Rogler, Ph.D.

To answer the question of what culturally sensitive mental health research is, the author focuses on the entire process of research. He argues that research is made culturally sensitive through a continuing, incessant, and open-ended series of substantive and methodological insertions and adaptations designed to mesh the process of inquiry with the cultural characteristics of the group being studied. Illustrations include pretesting and planning of research, collection of data and translation of instruments, instrumentation of measures, and analysis and interpretation of data. The insertions and adaptations ideally have a cumulative effect in rendering individual projects culturally sensitive and in building culturally informed research.

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The relevance of culture to mental health certainly has not been neglected (1-7), but to this day the general question of what culturally sensitive mental health research is remains unanswered. The question is particularly relevant to psychiatrists and other mental health researchers involved in cross-cultural studies or studies of minorities in the United States.

I shall argue here that no single specific act or set of

finite acts performed on research provides a complete answer to the question. In general, research is made culturally sensitive through a continuing and open-ended series of substantive and methodological insertions and adaptations designed to mesh the process of inquiry with the cultural characteristics of the group being studied. Considerations pertinent to the culture become an organic part of the process, every bit as important to the success of the research as are the more formal research procedures codified in epidemiology and clinical research textbooks. The insertions and adaptations span the entire research process, from the pretesting and planning of the study, to the collection of data and translation of instruments, to the instrumentation of measures, and to the analysis and interpretation of the data. Research, therefore, is made culturally sensitive through an incessant, basic, and active preoccupation with the culture of the group being studied throughout the process of research. Thus, my purpose here is to develop and illustrate a process-oriented definition of how mental health research is made culturally sensitive—not to analyze or codify specific techniques and approaches used for making research culturally sensitive. Such techniques and approaches are instances of the general process I seek to define.

In attempting to develop this general definition, I shall use some illustrations drawn from my own research on issues of mental health in Hispanic groups, although the general points that will be made apply equally well to research on other cultural groups and to topics that do not involve mental health. The use of my own research is due partly to the fact that decision making in the interest of cultural sensitivity often forms part of the unreported history of a research project. Such decision making is likely to remain only in the unpublished field notes or in the researcher's memory. The highly structured character of our professional publications does not encourage reporting of the

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petitious trials and errors, the confusing interactions, and the hard-earned increments of progress that occur in the effort to sensitize research to the culture of the study group.

To enlarge the scope of illustrations, I shall orient the discussion toward nonexperimental field research that is guided by an explicit theoretical model and that must contend with the measurement of concepts embedded in the model. Once again, however, the points that will be made are not restricted in their application to such research. Furthermore, since I advance the proposal that the attainment of cultural sensitivity is a continuing, open-ended process, the points illustrated do not represent a comprehensive statement of all the ways in which research can be made culturally sensitive.

RETESTING AND PLANNING

The pretest phase of field research customarily is devoted to the objective of polishing the instruments and ironing out the kinks in the research procedures. If this is the sole objective of pretesting, however, major components of the research problem may be inadvertently omitted. Culturally sensitive research requires an expansion of the pretesting objectives to include a period of direct immersion in the culture of the study group, preferably by means of the traditional ethnographic methods of participant observation and interviews with knowledgeable informants. The open-ended flexibility of ethnographic methods in attuning the researcher to the setting may well indicate a new focus for the research. For example, Hollingshead and (8), in a study of schizophrenia in families living in the slums and public housing developments of San Juan, discovered the importance of spiritualism as a socially supportive mechanism as a serendipitous result of using ethnographic methods early in the pretesting phase of the study. We heard emotionally disturbed persons refer to their symptoms using the nomenclature of spiritualism and interpret their maladies by means of spiritualist doctrine. We observed spiritualist mediums in the wards of the local asylum giving their special therapy designed to control the spirits of the patients. We accompanied persons psychiatrically diagnosed as schizophrenic on visits to spiritualist sessions to observe how their problems were interpreted and treated.

This discovery illustrates the goal of ethnoscience and other anthropological approaches to cross-cultural research (9–14): “the search for classifications of various domains in a culture, as seen by members of that culture” (15). Such classifications are referred to as “emic” because they are indigenous to the culture, as opposed to “etic” classifications, which form part of the general nomenclature of the psychiatrically oriented researcher. Thus, in the group we studied, spiritualism claimed competence in the interpretation and treatment of what were, in psychiatric terms, patho-

logical symptoms. If an individual reported delusions, the spiritualist told him or her that evil spirits were responsible for this malady. To the person living in a slum, this explanation was more credible than those premised on the intricate functions of the id, ego, and superego, all of which were concepts far removed from common experience and belief. The emic interpretations of such deviant behavior in Puerto Rican culture structured in important ways the life experiences of persons diagnosed as schizophrenic. As a serendipitous result of observations of the culture during pretesting, our study went on to produce the first empirical documentation of the pervasive therapeutic functions of Puerto Rican spiritualism.

If in-depth pretesting can indicate the need for unexpected insertions into the study, it can also sensitize the researcher to the problem of imposing a concept that is not applicable to the cultural setting. To illustrate, I return to our ethnographic pretesting experiences (8). The general issue to be examined was the relationship between a schizophrenic spouse and the structure of the marital union. In keeping with traditions established by students of the family, one of the initial ideas was to study the structure of marital unions by means of the concept of decision making. Spouses would be asked whether their partners prevailed in the making of decisions with respect to many different issues, the specific objective being to ascertain patterns of marital dominance. It was immediately clear that the items commonly used in U.S. studies to evaluate decision making—where to go on vacations, which school the children should attend, the purchasing of insurance policies, and so on—were not applicable to the impoverished Puerto Rican families we studied. However, we still had the option of modifying the items to suit the underlying concept of decision making. As pretesting proceeded, this option eroded away. It became clear that the concept of decision making presupposed a situation of choice, with each spouse bidding for his or her preference in a context of open and companionate marital communication. This presupposition did not fit these Puerto Rican families.

The Puerto Rican families we studied were at the very bottom of an economically impoverished society's stratification system, struggling to satisfy their most elementary needs for food, clothing, and housing. Their margin of choice and, therefore, of decision making was slim indeed. Instead of decision making, the critical concept was the division of labor between spouses in a cultural context that classified tasks as men's work or women's work. Complementarities in the division of labor between the spouses was the basis of family solidarity. The pretesting experience moved the focus of the study away from decision making and toward the issue of how schizophrenia shapes the allocation of tasks between the husband and the wife.

This change is an example of an attempt to avoid one of the consequences of what cross-cultural researchers who focus on issues of mental illness have labeled the “category fallacy” (16, 17). The fallacy

entails "the reification of a nosological category developed for a particular cultural population and the application of that category to members of another culture without establishing its validity for that culture" (16, p. 10). In cross-cultural psychiatry, the fallacy is most evident in the imposition on other cultures of clinical categories of mental illness, such as those in *DSM-III*, or of scales measuring dimensions of mental illness, such as the MMPI, without considering the question of whether they are applicable. It should be mentioned, parenthetically, that cultural validity is not established, nor is the category fallacy avoided, when culturally different respondents answer interview or questionnaire items presumed to reflect the concept under study, which often is taken as the standard in perfunctory pretesting of research. Once assigned the role of interviewee, respondents are expected to answer questions, and they will. The test of cultural validity involves, instead, the dialectical matching of the assumptions undergirding the concept and perceptions of the cultural setting to see if and how they fit.

Scholars representing the "new cross-cultural psychiatry," such as Kleinman (17) and Good and Good (16), have made instructive observations of the consequences of the category fallacy. If the cross-cultural researcher uses narrowly defined categories derived from the professional research culture, cultural variability may be suppressed. The appearance of cross-cultural homogeneity can be the artifactual product of the originally constricted definition of the category. Moreover, the measures used may only touch—if even that—the associated variability in culture-related symptoms expressed in the idioms of the culture. Kleinman's research (18), which demonstrates that the Chinese somatize depression much more than Americans do, calls attention to this problem. There is a need for research that departs from the prevailing, almost routinized *a priori* commitment to standing measures of mental health. Such research, which is more basic and much less often conducted, begins with the assumption that our ignorance is problematical, and it seeks to uncover the indigenous configuration of mental health problems and symptoms in the cultural group. The data produced by such research are essential if we are to have a culturally informed mental health policy for minorities.

Another way in which research is made culturally sensitive during the planning phase is through the explicit incorporation of concepts that are avowedly cultural into the study's theoretical formulations. For example, some years ago at Fordham University's Hispanic Research Center, we confronted the task of developing formulations attempting to link migration to mental health (19), since practically all of the Hispanics in New York City are first- or second-generation immigrants. We postulated that the concept of acculturation played a major role in the linkages between migration and mental health. Acculturation refers to the complex process whereby the behaviors and atti-

tudes of a migrant group change toward those of the host society as a result of exposure to a cultural system that is substantially different. Thus, the incorporation of such concepts into the theoretical formulations guiding research reflects sensitivity to the role that culture plays in shaping human adaptations to new settings (20).

Such formulations guide not only field-oriented research but also clinical research seeking to examine the effect of culturally based therapeutic modalities. A clear example is the research undertaken by Costantino, Malgady, and myself (21). We sought to test the impact of *cuento* therapy (folk tale therapy) on second-generation Puerto Rican children who, trapped between two cultures, were at high risk for mental disorder. *Cuento* therapy is a modeling technique based on the principles of social learning theory, but it takes as its clinical medium folk tales traditional to Puerto Rican culture and focuses them on acculturatively distressed children. The objective of the therapy is to transmit cultural values and foster pride in Puerto Rican cultural heritage while encouraging adaptive behavior to the host culture. The complexity of the objective reflects the complexity of the bicultural situation of the children. Our study provided empirical justification for the development of culturally based therapeutic interventions for the benefit of persons experiencing acculturative dilemmas (21). The main point is that culturally sensitive clinical research attempts to formulate hypotheses reflecting the intricate connections between cultural elements and the psychotherapies administered (22).

THE COLLECTION OF DATA AND THE TRANSLATION OF INSTRUMENTS

Beyond pretesting and planning culturally sensitive theoretical formulations, culturally sensitive research means that in the collection of field data the researcher makes adaptations to the respondent's cultural context. A study of intergenerationally linked Puerto Rican families in the inner-city neighborhoods of New York City, conducted by Cooney and myself (23), provides an example. The study required in-depth interviews with mothers and fathers in a parent generation and with sons or daughters and their spouses in a married-child generation. The interviewers' bilingual skills provided the respondents with the option of speaking either Spanish or English. Without this option, the data could not have been collected, because 91% of the parent generation group chose Spanish, while 75% of the married-child generation group chose English. This difference reflected corresponding differences in the two generations' acculturative levels as well as the higher educational status of the younger generation.

One of the important cultural amenities observed while interviewing the parent generation was the form of address: the second-person pronoun *usted* (or *señor*

señora, don or doña) was used. *Usted* connotes respect, establishes an appropriate distance in the relationship, and was a formally correct way for the younger interviewer to address the older respondent. With the younger couples, there was no need for the formal *usted*; the relationship was more informal, and the form of address was *tú*. With this generation, the interpersonal amenities were rooted in the similarity of age between interviewer and respondent and in the common cultural experiences of Hispanics in New York City. Adaptations to the two generations' cultural contexts enabled the interviewers to collect the data successfully.

The provision of a language option to a bilingual respondent and the translating of a study's instruments into the language of a monolingual respondent represent necessary and obvious steps toward culturally sensitive research. These adaptations, however, are hardly simple; rather, they represent the end result of a complex process of translation that is designed to approximate equivalence of meaning between the languages involved. In a study that reviewed 80 articles in two major publications for cross-cultural psychological research, Brislin (24) reported that over three-fourths of the articles "gave no information or such scanty information that translation problems could not be ruled out as a source of data contamination" (p. 187). In more recent years there have been some improvements in translation procedures (15), but it appears doubtful that there has been a substantial increase in general efforts toward the goal of culturally adapting psychiatric research.

A number of procedures have been developed to address the problem of increasing the equivalence of meaning between the languages being translated (15), but the most commonly used is the back-translation method. With this method, a bilingual person translates from the source language of the instruments (or the instructions for administering the instruments) to the target language, and then another bilingual person translates the material from the target language back to the source language. Comparisons are then made between the original material and the back-translated material. Discrepancies in the two versions, or translation errors, become the focal point for changes and adaptations in both languages. The objective is to "decenter" the language away from the source language into an equal linguistic partnership with the target language, so that both of the resulting versions are easy to read, smooth, and natural sounding. I have described the back-translation method in simplified form here, but one qualifier should be added: the decentering process does not eliminate problems of cultural bias. Bias may still be present because the framework that structures the decentering process is derived from the research concepts expressed in the source language. Emic elements in the target culture may be left by the wayside.

INSTRUMENTATION

The language of the interview, of course, is not the only cultural factor to consider in the conduct of culturally sensitive research. An effective translation sets the stage but does not resolve a host of measurement issues relevant to cultural sensitivity (5). One specific effort to recognize and account for cultural components in instrumentation has become centrally relevant to research in social psychiatry. It was presented in Dohrenwend's influential article published more than two decades ago (25). He argued that the relationship between social status and psychological disorder implicates issues of substance and issues of method. Issues of substance dealt with the explanation for the consistent finding of an inverse relationship between social class and psychiatric disorder: Are the social classes generative of psychological disorders in the lower class or is there a social selection process that disproportionately concentrates psychological disorders in the lower class? Dohrenwend argued that the importance of this substantive question must surrender precedence to measurement problems in assessing untreated psychological disorders. His argument, too intricate for a brief summary, concluded with a still unanswered question: "What are the cultural and situational factors that lead to different modes of expressing psychological symptoms?" (p. 34).

The question arose out of findings indicating that Puerto Ricans in the Washington Heights section of Manhattan reported a significantly greater number of psychiatric symptoms than did their social-class counterparts in other ethnic groups. However, other findings indicated that Puerto Rican respondents evaluated the symptom statements in the scales as less socially undesirable than did other groups, which, perhaps, led them to admit to more of them. The root issue is how cultural components that are viewed as conceptually extraneous to psychological distress intrude on the observed assessment of psychological distress. In this context, cultural sensitivity means that the influence of variables should be considered in the measurement of concepts, regardless of whether the concepts involve issues of mental health.

If Dohrenwend's argument is viewed according to the objectives of epidemiologic surveys of untreated psychological disorders, the problem posed is one of measurement error—the need to partial out the influence of cultural expressions on the measurement of psychological disorder. This procedure assumes that cultural expressions are analytically separate from psychological disorders, an assumption that implicates the emic-etic distinction. However, emic cultural expressions should not always be treated as contaminants of measures. They also play an important positive role in the psychometric development of scales by providing indigenous criteria for validation. An illustration of such validation is provided by the construction by Ir-

win et al. (26) of a test to measure the intellectual development of 7-year-old children in Guatemala. The construct validity of the tests was determined by examining the correlation between the test's seven components—such as picture vocabulary naming and the matching of familiar figures—and customary variables, such as socioeconomic status and school performance. The research is distinctive, however, in its creative use of the Guatemalan concept of *listura* as a cultural analogue of intellectual development. In Guatemalan culture, *listura* closely resembles what Americans view as brightness or quickness. *Listura* is a highly valued attribute and is used by Guatemalan villagers to classify each other. Accordingly, women in the same village as the children were asked to classify the children (with the aid of photographs of the children) in terms of how *listo* they were. The test's correlations with the construct validity measures were adequate, but the correlations with the indigenous classifications of *listura* were substantially higher. Indigenous validity added to the test's cultural sensitivity because it informed us about processes occurring specifically within the culture.

An even more highly developed illustration of this procedure was provided by Manson et al. (12) in their development of the American Indian Depression Schedule on the Hopi Indian Reservation of Arizona. Cultural validity was immediately addressed in the initial, open-ended ethnographic elicitation—and subsequent retesting—of the Hopi's mental illness categories by asking the respondent, What are the sicknesses or things that can be wrong with people's minds or spirits? (p. 336). Following the reply, one probe after another attempted to determine behavioral, affective, and cognitive dimensions of the indigenous illness categories; the perceived causation of the illnesses; the differences between the illnesses and what were the reasons for these differences; and the effectiveness of various forms of treatment. This procedure identified clusters of characteristics associated with the indigenous categories.

The next step incorporated into the development of the Hopi version of the American Indian Depression Schedule selected components of the *DSM-III*-based National Institute of Mental Health Diagnostic Interview Schedule (DIS) (27), which focuses on depression, somatization disorders, and alcohol-related behavior. The components were used only after being extensively revised to approximate Hopi English usage sociolinguistically and to differentiate meanings of concepts that in English can be used in a unitary fashion but cannot in Hopi culture. Other components of the DIS were developed to assess sociodemographic and experiential aspects of the culture. Finally, a clinic index group was selected by means of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (28) in the interest of establishing criterion validity in relation to a community group matched to the clinic index group in age and sex.

Even with this very brief description, one can begin

to forecast the culturally important questions the study sought to examine, questions that extend far beyond psychometric issues to a probing examination of how Hopi culture structures its views of mental health problems in relation to existing clinical concepts. This study by Manson et al. provides an illustration of carefully organized research seeking to interrelate emic cultural elements with etic concepts and procedures.

THE ANALYSIS AND INTERPRETATION OF DATA

The insertions and adaptations that are made throughout culturally sensitive research to integrate local cultural meanings with scientific categories (5) provide the basis for culturally sensitive analysis and interpretation of data during the last phase of the research. If the theoretical formulations guiding the research explicitly contain cultural variables, cultural sensitivity means that the analysis and interpretation of the data should give comprehensive attention to the operation of such variables. A psychiatric epidemiology study by Warheit et al. (29) is illustrative, even though it is based on preestablished measures of mental health and not on measures indigenous to the culture of the Mexican-Americans who formed part of the study group. The study proceeded from the general theoretical view that ethnicity and acculturative level in minority ethnic groups shape the distribution of psychiatric symptoms and dysfunctions (30). Depression, anxiety, and psychosocial dysfunctions were measured in two Mexican-American study groups and one group of Anglos.

Aware that cultural factors may influence the psychometric properties of instruments, Warheit et al. (29) first determined that the reliability (alpha) of each of the mental health scales was adequate in each of the groups studied. They then examined the impact of standard demographic variables on three dimensions of mental health in the entire sample and then in each of the subgroups. This procedure was based on the assumption that at the level of the total sample the impact of demographic variables could vary according to ethnicity and acculturative level. Warheit et al. then did a step-by-step analysis using the demographic variables, on the assumption that patterns of influence may vary according to ethnic group and acculturative level. Finally, they made intergroup comparisons, controlling for the demographic variables.

The overall pattern of findings of Warheit et al. tends to confirm what other studies have found: higher rates of symptoms among females than males; more symptoms among the Mexican-Americans than Anglos; and fewer symptoms among the more acculturated, English-speaking Mexican-Americans than their less acculturated, Spanish-speaking compatriots. The predictability of most of the findings adds credence to standing epidemiologic hypotheses but in no way diminishes the culturally sensitive analysis of data that

brings cultural concepts systematically to bear on issues of mental health.

The cultural sensitivity that guides data analysis generally merges imperceptibly into the final phase of research, the interpretation of data. At times, however, the concept of culture is explicitly and self-consciously introduced into the continuing interpretation of research findings. These instances are particularly instructive because they highlight processes that otherwise might remain unexamined. A clear illustration from cross-cultural research on the family is provided by Hyman's formulation of a theory of resources in cultural context based on contradictory findings on marital power (31). In its simplest terms, resource theory—a derivative of broader theories of exchange—asserts that the distribution of marital power favors whichever spouse brings the most resources, such as education, occupation, and income, into the marriage. Having examined research findings from nine countries, Hyman observed that studies in some of the more developed countries but not in the less developed countries supported resource theory. This prompted Hyman to develop a typology classifying countries according to four levels of social development: patriarchal, modified patriarchal, transitional equalitarian, and equalitarian. In the patriarchal countries, such as India, the pervasive uniformity of male-dominant cultural norms confers power on the husband. In equalitarian countries, such as Sweden, the pervasive uniformity of norms of equality between the sexes culturally mandates the sharing of power between spouses. The sex-oriented cultural norms in both types of countries are so widespread as to deny conjugal transactions the latitude required for the spouses' respective resources to come into play to shape the distribution of marital power. Thus, resource theory applies to neither type of country at the extremes of the typology.

The national cultures in the two types of countries in the middle ranks of the typology suffuse the factors associated with resources with different meanings. In the modified patriarchal countries, such as Greece and Yugoslavia, the resource factors signify the location of persons and their families in the socioeconomic system. Those who are higher with respect to such factors, who are in the vanguard of modernizing changes, more quickly accept the introduction of egalitarian norms and are taking a step away from patriarchal traditions. For this reason, findings from these countries, contrary to the predictions of resource theory, show an inverse correlation between the husband's command of resources and his marital power. In the culturally flexible, transitional equalitarian societies, such as the United States and West Germany, the resource factors signify not only socioeconomic position but points of leverage in the power exchanges between the spouses. In these countries, marital power increases with increases in resources. Here, resource theory applies. Hyman's success in bringing conceptual order into a disarray of cross-cultural findings was a result of

rooting resource theory into the typology's appropriate cultural contexts. The broader theory has demonstrable cross-cultural importance and has been useful in explaining intergenerational changes in marital power among first-generation immigrants and their married offspring (23). Sensitivity to culture in the interpretation of findings can suffuse concepts with new meanings in such a way as to increase the generalizability of theoretical explanations.

DISCUSSION

The general question of what culturally sensitive research serves as a healthy reminder of the middle-class ethnocentrism that still permeates much mental health research. However, earlier in this paper I disavowed the common expectation that a single operation or a delimited set of finite operations performed on research would provide a complete and general answer. The question often is posed as if such an answer could be given. Consequently, answers to the question tend to focus exclusively on some specific technique, as if the use of the technique comprehensively fulfilled the complex requirements of cultural sensitivity. In research projects with bilingual, bicultural populations, the technique customarily invoked is the back-translation method, a procedure that has almost assumed the character of an orthodoxy. To a large extent, this method has been codified, and it is capable of replication in the production of tangible results. It fulfills the researcher's understandable desire to operationalize procedures explicitly so as to render them publicly available to the community of other scholars. Yet, as important as it is, it represents only a step in the direction of cultural sensitivity.

I believe the problem stems from an impoverished theory of the role of culture in human life and how to account for it in research. For example, Kleinman (17) has noted that in traditional cross-cultural psychiatry the category fallacy is closely tied to the assumption of "disease as an entity, a thing to be 'discovered' in pure form under the layers of cultural camouflage" (p. 4). He concluded that "there can be no stripping away of layers of cultural accretion in order to isolate a culture-free entity" (p. 4). Since culture does not layer human life, nor leave its residues in a finite array, there can be no set number of procedures to answer the general question of how research is made culturally sensitive. Culture penetrates human life in multitudinous ways, some of which we are beginning to understand but most of which still remain to be discovered.

It follows that culturally sensitive research encompasses much more than translation procedures and much more than an attempt to correct the mischief resulting from the category fallacy. I propose that when research projects or programs of research that claim to be culturally sensitive are explained and the decisions made are justified, systematic attention must be given to the question of how the cultural character-

istics of the study group pervasively shape the entire course of inquiry. The attention given to this question, in the context of cross-cultural research or research focusing on cultural minorities, is every bit as important as the customary attention given to related methodological issues such as sample selection, the psychometric properties of instruments, or data analysis techniques.

I propose also that if we are to avoid culturally based misunderstandings in mental health research, the drive toward culturally sensitive research should attain importance across the entire spectrum of epidemiologic and clinical service research. The attainment of such sensitivity, in fact, remains troublesome in studies of the life circumstances giving rise to emotional distress, how such distress prompts help-seeking efforts by the afflicted and their significant others, the institutional pathways persons follow as they seek help, the convergence of sociocultural forces on the evaluation of mental health status, the intricate adaptations of therapies to patients, and the effectiveness of such therapies in enabling patients to resume their customary social roles (32). If these clinically relevant processes are seen in the context of the cultural pluralism in the United States and cross-national cultural variability, the pressing need for making research culturally sensitive becomes evident.

In sum, cultural sensitivity in research means the incessant and continuing finely calibrated interweaving of cultural components and cultural awareness into all phases of the research process. Illustrations of this have been provided in the pretesting and planning of research, in the collection of data and translation of instruments, in the instrumentation of measures, and in the analysis and interpretation of data. Other illustrations, arrayed across all of the phases of research, could just as well have been provided. Since the research process ideally is cumulative, each phase contains the residues of the previous phases' culturally sensitive insertions and adaptations. Since research also is cumulative in the larger sense that one research project builds on the experiences of previous research projects, there should be—in an ideal sense—an ever-expanding sensitivity to the role of culture in research. One can no more foresee the terminal point in this drive toward culturally sensitive research than one can predict a ceiling to the development of social psychiatric theories and methodologies. The two are inextricably intertwined.

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Legal Principles in the Psychiatric Assessment of Personal Injury Litigants

Brian F. Hoffman, M.D., F.R.C.P.(C), and Harvey Spiegel, B.A., LL.B.

The authors review the legal principles that a psychiatrist must understand in assessing the emotional and psychiatric sequelae of a personal injury leading to a litigation claim. The principles of the establishment of fault or liability, the assessment of pain and suffering, causal connection, the credibility of the plaintiff, the credibility of the expert witness, the determination of prognosis, the award of damages, and the adversarial system are discussed. An appreciation of these principles will enable psychiatrists to provide assessments that will be useful to the legal system in arriving at a fair and accurate determination of the compensation to which a victim is entitled.

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In a previous paper (1), one of us (B.F.H.) described the outline of a psychiatric medical-legal report that would be useful to insurance companies, lawyers, and courts in understanding the emotional consequences of a personal injury proceeding to litigation. In this paper we look beyond the medical-legal report to examine the relevant legal principles applied in assessing claims arising out of such injuries. The psychiatrist must have at least a rudimentary understanding of the legal framework within which a victim's claim for compensation is to be resolved if there is to be a satisfactory interplay between the lawyer and the psychiatrist in dealing with the claims of victims who have suffered psychic injuries or other emotional consequences of torts.

A tort is a civil wrong, as opposed to a criminal wrong, perpetrated by one citizen against another (2, 3). The word "tort" is derived from the Latin *tortus*, which means twisted or wrested aside. The most common modern examples are motor vehicle negligence, product liability, and professional malpractice. Less common examples include negligence, invasion of pri-

vacy, defamation, misrepresentation, nuisance, assault and battery, and false imprisonment. Many torts may result in physical injuries that may or may not be accompanied by psychic or emotional trauma. Since the 1940s, disability from a nervous or mental disorder has been recognized by the courts in North America as compensable when accompanied by a physical injury (4). More recently, some courts have recognized the existence of psychic or emotional trauma in the absence of any physical trauma—for example, witnessing an injury to a co-worker (4, 5), stress at work (4), or the emotional trauma associated with unlawful dismissal from work. One estimate is that approximately 2%–3% of torts are associated with psychiatric disability (2). Psychiatrists are increasingly being asked to assist the courts in evaluating the cause, extent, and severity of emotional reactions that appear to follow a wide variety of injuries. By understanding the relevant principles of law, psychiatrists who are retained by the plaintiff, by the defense, or as consultants to the court will comprehend the specific legal questions at issue and conduct an examination and prepare a report that addresses these questions in a professional, comprehensive, and objective manner.

FAULT OR LIABILITY

Under the laws in most states of the United States and provinces in Canada, damages will be awarded if the plaintiff can establish negligence or some other wrongful act or omission on the part of the accused that results in injury to the claimant (2). Negligence is not defined in terms of intent or state of mind but, rather, as "conduct which falls below the standard of care established by law for the protection of others against unreasonable risk of harm" (2). In the vast majority of cases, the issue of fault or liability is clear—for example, loss of control of a motor vehicle caused by impairment of the driver, a rear-end collision, or failure to obey a stop sign. In other cases, the issue of liability may not be so clear and a great deal of time may be spent in determining who is at fault or liable for the casualty—for instance, two drivers each making left-hand turns or a collision at an intersection without stop signs. In some cases, liability may be found to lie with both parties. In most jurisdictions, if

Received Sept. 3, 1987; revision received April 12, 1988; accepted May 26, 1988. From the Division of Inpatient Psychiatry, Mount Sinai Hospital, Toronto, the Faculty of Medicine, University of Toronto, and Green and Spiegel, Barristers and Solicitors, Toronto. Address reprint requests to Dr. Hoffman, Rm. 931, Department of Psychiatry, Mount Sinai Hospital, 600 University Ave., Toronto, Ont. M5G 1X5, Canada.

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there is a finding of contributory negligence against the claimant, the claimant's recovery of damages will be reduced by the percentage of his or her fault. For example, if an injured man is found to be 25% responsible for an accident, then the amount of his recovery of monetary damages is reduced by 25%.

In the context of a damage claim for the emotional consequences suffered by a claimant, the plaintiff must prove that there is another party who is the cause of the claimant's misfortune. However, the role of the injured party or victim is often maintained by a complex multiplicity of factors. Psychiatrists, aware of the complexities behind human behavior and motivation in a claim for compensation, should be skeptical of simplistic explanations and outrageous demands (6). Some plaintiffs will blame all manner of problems and difficulties on a minor accident. Care should be taken to distinguish those traumatic situations which produce true psychiatric complications from situations in which the injured party mistakenly attributes all of life's problems to a specific injury (3). On the other hand, a substantial proportion of patients who have severe or prolonged emotional reactions after a motor vehicle accident may minimize their pain or disability or have difficulty expressing their anger directly about the person who caused the trauma or injury. Some victims of crimes or motor vehicle accidents may have difficulty pursuing a claim because they feel unreasonably guilty, believing they could have prevented the trauma if only they had done something differently. Some plaintiffs have difficulty establishing negligence because they are consumed by excessive guilt or anger. On the other hand, in some complicated claims the victim believes he or she is faultless in the accident but the defendant alleges that the plaintiff may have contributed to the accident, which subjectively adds insult to injury and further complicates the victim's emotional recovery.

PAIN AND SUFFERING

The courts are now beginning to look beyond physical injuries and disability and to consider subjective experiences of injury such as emotional pain and suffering. Psychiatrists are called on to assess patients who complain of severe and continuous pain and suffering with no apparent physical cause. Patients may fear that, in finding no physical cause, other medical doctors are saying that their experience is not "real pain" like the pain resulting from an organic injury.

Psychiatrists, in assessing these patients and writing their report, must make it clear that patients suffering from emotional injuries resulting in psychogenic pain, anxiety, or depression are going through as real an experience as the patient who has physical pain caused by fractured bones and torn ligaments.

Lay people and the courts can readily understand how a physical injury can lead to disability, but they have more difficulty understanding how disability can

be caused by an emotional reaction to a physical injury that would not by itself cause disability. Even more difficult for the lay person to understand is how a purely emotional trauma can cause disability. Psychiatrists can make it clear that such a disability is as real and natural a consequence of trauma as is a physical injury. They should describe in the report, and later in testimony, in terms that can be easily grasped by a lay person, how the mind and body are intertwined and the mechanism by which a disturbance to the emotional balance of an individual can translate itself into physical symptoms and disability.

CAUSATION

The issue of causation is crucial in the resolution of a claim for compensation. The claimant is entitled to recover damages only for those problems which are caused by the defendant's wrongful act. In nonlegal clinical work, psychiatrists and other medical practitioners may not be as concerned about the cause of a patient's problem as determining the nature of the problem and recommending management. However, lawyers are called on to establish the causal connection between an accident and an injury. What the plaintiff's lawyer requires from the psychiatrist is an opinion on whether the problems experienced by the patient are a direct result of the wrongful act of the defendant. This is a conclusion that psychiatrists may be reluctant to draw because they are aware of a variety of predisposing, precipitating, and perpetuating causes of the patient's symptoms. Defense lawyers will try to find and emphasize factors unrelated to the specific trauma that may have caused the emotional suffering. They will try to prove either that the emotional symptoms or disability would have occurred without the accident or that the symptoms are the result of the patient's conscious exaggeration or fabrication.

The relationship between an injury and the subsequent emotional reaction is not usually that of simple cause and effect. Severe emotional reactions after minimal physical injury appear to be more common with a sudden unexpected accident or when there are only a few seconds of warning, particularly when defensive action is blocked or is totally irrelevant (3). This is especially true when the accident occurs in a safe and familiar environment such as one's own car (3). Psychiatric consultants will have to assess whether the nature of the traumatic event was so severe that a particular result (for example, a phobic reaction to cars) would develop in most healthy individuals in these circumstances or whether some degree of personal vulnerability was present that would account for the extent or duration of the emotional reaction. Psychiatrists recognize that emotional symptoms and disability can be influenced by a variety of factors, such as genetic and constitutional factors, family attitudes and circumstances, and the wish to be looked after and cared for (5, 7). There is general agreement that the

slower the litigation process, the more likely it is that psychological complaints will continue (5). Unfortunately, an award of monetary compensation at the conclusion of the litigation process does not reverse the disability in most patients, and they may continue to suffer interminably.

There is an important legal principle that simplifies the determination of causal connection for the purposes of awarding compensation. The "thin-skulled man rule" basically says that if you hit a man with a thin skull over the head, you cannot successfully resist a claim for the greater damage you caused because of the thin skull by saying that if the victim had had a normal skull he would not have suffered as severe an injury. The law says the wrongdoer must take his victim as he finds him (5). In the context of a man with an emotional injury, the defendant is not entitled to say, "I am not responsible for compensating the plaintiff for his depressive reaction to this accident because he was already psychologically fragile and full of unresolved conflicts. Had he been more psychologically healthy to begin with, then the accident would not have caused such severe emotional consequences." There is no difference in principle between the thin skull and the eggshell personality. If it were otherwise, there would be few cases in which a claimant who had suffered an emotional injury could be successful in a claim for damages, because in most cases there are contributing causes, either in the premorbid personality or in the concurrent life stresses. As long as the psychiatrist is able to express the opinion that the accident or trauma was the *proximate* cause, in the sense that the problem would likely not have occurred but for the trauma, the requirement of legal causation has been satisfied (5, 7). In other words, the psychiatrist should try to answer the question, But for the trauma, would the emotional disturbance for which compensation is sought have occurred? If the answer is, Probably not, then the claimant is entitled to be compensated. On the other hand, if it is demonstrated that there was a pre-accident vulnerability in the plaintiff's mental constitution such that he or she would probably have developed a similar kind of emotional problem sooner or later, even if the accident had not occurred, then the plaintiff will fail in this aspect of his or her claim or may recover damages only to the extent that the trauma accelerated the condition.

CREDIBILITY

It is essential that psychiatrists take and corroborate a very thorough and complete history so that they can express an opinion as to the cause of a patient's emotional suffering and/or disability and so that the lawyer can be confident in that opinion. This history is important from two points of view. First, the defense lawyer will be seeking to attribute the cause of the patient's problems to factors other than the accident. For example, if the patient had gone through a marital

breakdown, suffered severe financial problems, had death in the family, or experienced some other emotional trauma not connected to the accident, the defense lawyer would argue that these events caused the plaintiff's emotional problems and that the plaintiff would have these problems even if the accident had not occurred. Psychiatrists should not form an opinion about causation without carefully exploring all possible causes of the condition. A competent defense counsel will usually investigate the plaintiff's background and will at some point examine the plaintiff under oath, before trial, to try to uncover the existence of other causes for the plaintiff's condition. Psychiatrists who fail to inquire carefully into the patient's history are very vulnerable when faced with the task of supporting their diagnosis under cross-examination. The defense lawyer may raise possible predisposing or precipitating events of which the psychiatrist was not aware when conducting the assessment. Psychiatrists who have not taken a careful and complete history before forming their opinion are, of course, to blame for failing to note these possibilities. Thus, their credibility and the reliability of their opinions are jeopardized.

If, on the other hand, the psychiatrist has made the inquiry but was misled by the patient, then, of course the credibility of the patient comes into question (6). The issue of credibility is central to most personal injury claims in which there is no objective evidence of injury, as in posttraumatic stress disorder. The indicators of emotional suffering and disability are largely subjective and can be exaggerated or fabricated by an artful and dishonest claimant, although it is our experience that conscious exaggeration or fabrication is very rare. However, if the plaintiff appears to be honest both to the psychiatric consultant and to the court and the plaintiff's credibility cannot be shaken, it is very difficult for a defense counsel to successfully attack the diagnosis of any psychiatric condition that follows an accident. On the other hand, if the plaintiff gives the impression of being less than honest and appears to be making a conscious attempt to exaggerate symptoms or to conceal the fact that he or she had problems before the accident, then the defense counsel will be able to attack the plaintiff's credibility.

Plaintiffs who deny any and all difficulties or unhappiness in their lives before the accident or who attempt to hide previous periods of disability or compensation claims bring into question their credibility on other issues that are important in forming a diagnosis. However, the fact that they may have been in other accidents, previously injured the same parts of their bodies, or had psychiatric treatments previously for similar conditions does not disentitle plaintiffs to compensation if the accident aggravated the condition or activated a previously quiescent condition. In fact, such predisposing events or preexisting conditions may help the court to understand why patients had more severe or prolonged reactions than would ordinarily be expected. Indeed, the claim may be supported by previ-

ous psychiatric problems as long as there was a reasonable expectation that these problems would have been under control and would not have developed into the present pain or disability had it not been for the accident. It is not the history of previous events or preexisting conditions that seriously prejudices the plaintiff's claim but, rather, the plaintiff's attempt to conceal them.

In court, psychiatrists who have not taken a thorough clinical history from the patient or have not included important facts in their report give defense lawyers an opportunity for a twofold attack. First, they can attack the credibility of psychiatrists on the basis that they did not have a full history and were not aware of some very important contributing events that might have altered the diagnosis and etiological formulation (7). Second and perhaps more important, they can attack the credibility of the patient. If the patient is not truthful or is attempting to fabricate or to mislead, then the consultant's conclusions may be open to serious question. It is likely that psychiatrists are not astute at picking up true malingering if the patient is consciously inventing or exaggerating symptoms for financial gain (6). In some cases, nonmedical investigations, including surveillance, may have more to offer in proving this diagnosis (5).

PROGNOSIS

The courts require evidence regarding the effect of the alleged injury in the patient's life, including a projection into the future. A detailed history of what the patient was like both before and after the trauma is important not only to support the diagnosis and the question of causation but also in illustrating in graphic terms the extent of the loss of enjoyment of life, the changes in the personality, the family problems, and the mental torment resulting from the trauma. As in physical medicine, the degree of emotional disability is best described for the courts as a percentage of normal functional ability in the major areas of life—for example, work, family life, and sexual activity (7).

An award of damages in most common law jurisdictions in North America is once and for all. That is to say, the injured claimant is entitled to only one award of damages; once the judgment is granted or settlement reached, that is the end of the matter for all time. Plaintiffs cannot come back later and say that the physician's prognosis at the time of the settlement or trial was too optimistic or that they suffered a severe relapse after the trial had taken place and are now totally disabled. Settlements and judgments in personal injury cases are final and with the rarest exceptions cannot be varied even if the circumstances drastically change. Because of the principle of finality, the question of prognosis, especially in the more serious cases, becomes crucial. The average personal injury case comes to trial 2–5 years after the accident. In many cases the patient is still suffering from serious symp-

toms at the time of trial, so the task falls on the court to predict what the future will hold for the claimant. For emotional symptoms and disability, lawyers and courts will have to rely heavily on the opinion of psychiatrists and other medical experts. Although in clinical practice it is appropriate to be optimistic in speaking to patients regarding their prognosis in the hope that it may be a self-fulfilling prophecy, in the medical-legal context experts must be prepared to address the question of the future with great care in order to arrive at a *realistic* prognosis. If it turns out that the prognosis is too optimistic and the award is decided on the basis of that prognosis, the patient will suffer serious financial loss as a result. It is not unusual to see this type of prognosis expressed by surgeons who have operated on a patient and are then reluctant to admit that their handiwork may be less than a total and permanent cure of all the patient's problems. Similarly, psychiatrists should not overestimate the curative effect of time and psychotherapy. Experts should make themselves aware of follow-up studies of posttraumatic states.

Most people are aware that, in a criminal case, guilt must be established beyond a reasonable doubt. However, the standard of proof in a civil case is that of the balance of probabilities. In order to satisfy this standard the court must find that it is more probable than not that a certain fact exists or that an event occurred. Putting it another way, if, after weighing the evidence on a certain factual issue, the court felt the scales were evenly balanced, then establishing the fact will have failed. The court will treat the fact as not having been proven for all purposes. If, however, the court finds that the evidence supports the existence of the fact by a very slight margin (at least 51%), then the fact is taken to have been established for all purposes.

For example, when the issue of causation is contested, the conflicting opinions of experts have to be assessed by the courts. If, after weighing the evidence, the court is at least 51% certain that accident was the cause of the problems suffered by the claimant, then that issue of fact is determined in favor of the claimant as if it had been established with absolute certainty. In this case the claimant will be entitled to full compensation for his or her injuries.

However, when the court is considering the claimant's *future* problems, it will take into account possibilities as well as probabilities. For example, if the court concludes that there is a 20% chance of the claimant suffering future employment disability, then the claimant is entitled to damages on this account. The amount of this award will be influenced by the expert's opinion as to the likelihood of the event occurring. A psychiatrist will often be asked to express an opinion on prognosis in terms of percentages that assist the court in the calculation of monetary damages. Before giving evidence in this area, the psychiatrist should be familiar with the follow-up studies for various posttraumatic syndromes, such as treated and untreated major depression (8), minor head injury (9),

and cervical sprain (10), so that percentages can be assigned to the different outcome possibilities. The likelihood of improvement after the litigation claim is settled has also been investigated and reported in the literature (11, 12). The outcome percentages found in the literature will be modified by the relative importance of specific factors in the patient's history, nature of the injury, and response to treatment so far.

DAMAGES

In all cases, an attempt must be made to determine the proper sum of money to fairly compensate a victim for the injuries sustained. The basic principle of the law of damages is *restitutio in integrum*: the award should attempt to restore the plaintiff, as far as money can, to the position he or she would have been in if the accident had not occurred. It is only just that the victim of a wrongful act should, if at all possible, be made whole by the wrongdoer. In many cases, this is not a difficult objective to achieve; for example, if a victim is disabled and unable to work because of an injury, it is usually easy to determine the amount of the loss of income and compensate for it. Similarly, victims can be adequately reimbursed for out-of-pocket expenses for medical, hospital, and related services. Having been reimbursed for those expenses, the victim is restored to the same position financially as if the accident had not occurred. In these cases, the intervention of a lawyer is generally not required and the claim is usually settled between the individuals involved and the insurance adjuster directly. Difficulties arise, however, in those cases where there are real yet intangible losses such as pain and suffering, the loss of enjoyment of life, or loss of future income to which the court must attach a monetary figure.

Many jurisdictions permit recovery of damages for the loss of care, guidance, and companionship of a relative. From a psychiatric perspective, it is quite a complex task to assess the extent and severity of such a loss. It requires a careful exploration of the relationship that existed between the injured person and the relative before the accident compared with the relationship during the posttraumatic state to determine the consequences for the relationship and the emotional health, loss, and disability of the relative. Although this is a relatively new area of litigation, the courts are beginning to recognize the reality of the indirect effect of psychic trauma on family members. These claims can be quite substantial—for instance, when a spouse or parent becomes chronically depressed as the result of a motor vehicle accident and this adversely affects other family members by impairing the quality and nature of the relationship between the injured person and the affected family members. In these cases the courts must often rely heavily on the expert testimony of psychiatrists.

THE ADVERSARIAL SYSTEM

All of the issues discussed here are eventually settled in a legal framework that is essentially adversarial. Much criticism has been leveled at the adversarial system of conflict resolution, described in terms such as "gamesmanship under the gavel" and "the sporting theory of justice" (13). It has been said that a trial is not an investigation but a demonstration which evaluates only the selected evidence brought forward according to predetermined norms (13). A lawsuit has the primary purpose of settling a controversy between two parties without physical conflict and only secondarily looks for truth. Lawyers develop a loyalty to their clients that may sometimes conflict with the loyalty to truth. Evidence that is harmful to a client's case will be ignored, discarded, or discredited by a lawyer but of course will be sought for and adduced by the opposing counsel if it is helpful to that case. Thus, the adversarial system will usually arrive at the truth and result in a fair and just resolution of the conflict. Although most psychiatrists would prefer to act as unbiased consultants to the court, the legal arena assumes that witnesses are partisan and have some degree of bias (14, 15). Certainly, differences of opinions from psychiatric experts underline both the inexact knowledge base of our profession and the presence of conscious or unconscious bias in favor of the side that has retained the psychiatric consultant (14). Slovenko (15) stated that the expert "who takes a neutral role does his party a disservice, for the opposing party's expert will undoubtedly assume his role as advocate and his advocacy will go without challenge. Hence, a witness . . . is expected to do so under the terms of the adversary system or he should not participate." On the other hand, the American Medical Association (16), the American Academy of Psychiatry and the Law (17), and some medical disciplinary colleges (18) have adopted the position that expert psychiatric witnesses should be impartial and unbiased in their examinations and reports. Although some psychiatrists function as "hired guns" (14, 19), most psychiatrists would prefer to conduct an unbiased examination and let the lawyer decide whether to use their testimony.

Although psychiatrists may try to conduct an unbiased interview and give a fair and impartial report, they can expect to be challenged about their observations, opinions, and conclusions in cross-examination. Expert witnesses can also be asked hypothetical questions or may be asked if additional evidence that has been revealed during a hearing modifies their diagnosis or prognosis.

The adversarial approach, which involves cross-examination, testimony from opposing experts, and judgments from either impartial judges or nonmedical peers of the plaintiff, is difficult for most psychiatrists. A close parallel in a medical context would occur in a coroner's inquest or a clinical pathological conference that examines surgical decisions critically. However, the scientific basis of psychiatric

knowledge and practice is neither fixed nor universally agreed on; therefore, the observations and conclusions of any one expert are open to honest debate and even disagreement.

Even if the courts assume some degree of bias, we urge psychiatrists to be as thorough, impartial, and professional as possible whether they act for the defense or the plaintiff. In fact, to appear to have an obvious bias is to undermine one's own credibility and perhaps the credibility of the patient and therefore will be harmful rather than helpful to the case of the party on whose behalf the psychiatrist has been called.

Nevertheless, the questioning of one's credentials, observations, and professional opinion in open court is anxiety provoking and far removed from the usually private patient-doctor relationship. Fortunately, the psychiatrist can often learn something from this kind of battle of wits not unlike the learning process at a coroner's inquest. On the other hand, the psychiatrist has the opportunity to teach lawyers and courts much about the development of human emotions and how they can be affected by injuries and their sequelae; this role alone is important to society.

SUMMARY

It is important to remember that the goals of lawyers who hire psychiatrists and the goals of the psychiatric consultants may be different. The task of the lawyers is to present their clients' cases in the most favorable light in the adversarial arena. Most psychiatrists would see their task as to complete a comprehensive, balanced, and unbiased consultation as medical specialists. Once again we would argue that the interviews and reports of psychiatrists hired by either the plaintiff's lawyer or the defendant's lawyer should be comprehensive, objective, and balanced (1, 9). In most cases the facts collected by different but competent psychiatric consultants should be similar, although there can be honest differences of professional opinion on the weight to be assigned to the salient facts.

In the medical-legal assessment of a personal injury case, the usual psychiatric clinical issues of symptom diagnosis, treatment plan, and understanding the meaning and impact of events on the person are important. In addition, however, special attention must be paid to the relevant legal principles involved in establishing fault, determining proximate cause, assessing credibility, and estimating a realistic prognosis.

Although establishing fault or liability is not usually an important part of the psychiatric assessment in a personal injury case, it can become an issue when the plaintiff appears to be underreacting or overreacting to the litigation process. Pain and emotional suffering may be ignored or poorly described and documented by other medical practitioners. Other physicians may describe a physical injury but neglect how it affects a patient's psychological, family, and social life. The

psychiatrist, as a specialist in psychological medicine, must draw attention to the unity of mind and body, a fact that is too easily overlooked by many courts and lay people.

On the issue of causation, psychiatrists must assess the nature and degree of impact of a specific traumatic event on the life of a patient while understanding the importance of biopsychosocial multideterminism. If justice is to be served, the psychiatrist should neither overestimate nor underestimate the role of a specific physical and/or emotional event in the present and future life of the plaintiff. Specifically, the psychiatric consultant must address the question of whether the accident was a proximate cause of the subsequent symptoms or disability.

Credibility is an important issue for the courts. Only a thorough history and a comprehensive unbiased report will put psychiatrists in a position where their conclusions will be trusted by the court.

In the legal arena the prognosis should be as realistic as possible and supported by follow-up studies. Unrealistic optimism can prove to be a financial disaster to the disabled patient.

The adversarial approach in the legal system can be justified and must be tolerated because of the inexact nature of psychiatric knowledge and opinion. The psychiatrist can both learn from the process and help to educate the judicial system about the importance of emotional consequences of accidents in the context of a personal injury claim.

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Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Oct. 6 and Dec. 7, 1988.

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Pathophysiology of HPA Axis Abnormalities in Patients With Major Depression: An Update

Roger G. Kathol, M.D., Richard S. Jaeckle, M.D., Juan F. Lopez, M.D.,
and William H. Meller, M.D.

Four hypotheses have been proposed to explain why nonsuppression on the dexamethasone suppression test occurs in patients with major depression. These include 1) increased metabolism of dexamethasone, 2) decreased sensitivity of pituitary glucocorticoid receptors to dexamethasone, 3) hyperresponsivity of the adrenal gland to ACTH stimulation, and 4) increased central drive of the pituitary from hypothalamic/limbic structures that overrides the action of the dexamethasone. A critical review of the literature suggests that the last hypothesis is most closely supported by the data. Despite this conclusion, factors other than depression may be involved in hypothalamic-pituitary-adrenal axis dysfunction.

(Am J Psychiatry 1989; 146:311-317)

The central focus of research to answer questions concerning the pathophysiology of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with major depression has been related to dexamethasone feedback, since the dexamethasone suppression test (DST) is the most widely used tool for investigating the HPA axis in psychiatric research. Although the DST is only one of many instruments that can be used to identify HPA axis abnormalities, it provides a suitable springboard to understanding HPA axis abnormalities in patients with major depression. The principal hypotheses proposed to explain DST nonsuppression in patients with depression have been that there is 1) increased metabolism of dexamethasone in patients with major depression, which results in less dexamethasone available to suppress ACTH production at the pituitary (1-4); 2) decreased sensitivity of pituitary glucocorticoid receptors to dexamethasone,

resulting in less ACTH suppression and cortisol elevation (5-8); 3) hyperresponsivity of the adrenal gland to ACTH stimulation, resulting in continued cortisol secretion despite moderate significant ACTH suppression with dexamethasone (7-12); 4) increased central drive of the pituitary from hypothalamic/limbic structures, which overrides the action of the dexamethasone (10, 13-15); and 5) a combination of the previous hypotheses.

INCREASED DEXAMETHASONE METABOLISM

Each of these potential explanations for DST nonsuppression implies that there may be changes at different points in the feedback loop or, alternatively, that no abnormalities are present in HPA axis activity. For instance, if dexamethasone is metabolized before it reaches the pituitary, normal HPA axis function may, in fact, be present but may not be apparent because suppression with dexamethasone did not actually occur. If this is true, then one needs to explain why, in patients with depression, dexamethasone would be metabolized more rapidly and to determine if other findings related to the HPA axis are consistent with this possibility.

It is not surprising that numerous investigators (1-4) have found that dexamethasone levels in DST nonsuppressors are lower than those in DST suppressors. Meikle et al. (16) established such an inverse curvilinear relationship between postdexamethasone cortisol and dexamethasone levels in the normal population as well. The real question is whether the curve has been shifted up and to the right. The latter would suggest that for a given level of dexamethasone there is a higher postdexamethasone cortisol level, as has been shown in patients with Cushing's disease (17), or that suppressing levels of dexamethasone are truly not being achieved. Data by Carroll et al. (13), who tested four patients with depression before and after recovery, suggest that there is something about the depressive state which alters the cortisol responsivity to dexamethasone. To our knowledge, follow-up studies with a similar design have not been performed. In a comparison of normal control subjects and patients with depression, Johnson et al. (4) showed that all 15 con-

Received Dec. 14, 1987; revision received April 12, 1988; accepted Oct. 6, 1988. From the Departments of Psychiatry and Internal Medicine, University of Iowa; the Department of Psychiatry, University of Wisconsin, Madison; and the Department of Psychiatry, University of Michigan, Ann Arbor. Address reprint requests to Dr. Kathol, Department of Psychiatry, University of Iowa, Iowa City, IA 52242.

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control subjects who had dexamethasone levels less than 10 nmol/liter (40 ng/ml) suppressed 8:00 a.m. cortisol levels to below 140 nmol/liter (5 µg/dl), whereas 13 of 39 patients with major depression failed to suppress below that level. This finding has been replicated in a larger cohort by Poland et al. (18). These data suggest that increased dexamethasone metabolism (lower plasma dexamethasone levels) does not totally explain the reason for dexamethasone nonsuppression in major depression.

Using increased metabolism of dexamethasone as the sole explanation for DST nonsuppression is also not consistent with the fact that in some patients with depression, dexamethasone doses of up to 8 mg/24 hours are insufficient to suppress cortisol production (19). Further, increased metabolism of dexamethasone or, for that matter, increased metabolism of other glucocorticoids in the HPA feedback system does not explain abnormalities related to HPA axis function in depression. These abnormalities include a blunted ACTH response to corticotropin-releasing hormone (CRH) (11, 12, 20–22) and insulin-induced hypoglycemia (10); an elevated 24-hour ACTH and cortisol rhythm (23–26), increased CSF CRH levels (27, 28), or a trend toward these abnormalities in depressed patients who are DST nonsuppressors (29), an augmented cortisol response after administration of exogenous ACTH (7, 8, 30), or elevation of urinary cortisol in patients with active depression (31–33) and even after recovery (34).

GLUCOCORTICOID RECEPTOR SENSITIVITY

Decreased dexamethasone (or other glucocorticoid) receptor sensitivity at the pituitary is consistent with DST (31, 32, 35–39) and ACTH (40) nonsuppression and would also explain why there is an elevated diurnal pattern of plasma ACTH and cortisol levels (23–26) and an elevation of 24-hour urinary free cortisol (31–33) in patients with depression. The ACTH/corticotat in this case would be reset such that higher levels of cortisol would be necessary for feedback inhibition. Decreased dexamethasone receptor sensitivity would also be compatible with the finding that some patients with depression have resistance to as much as 8 mg of dexamethasone per day (19).

Despite the consistency of this hypothesis with several existing findings in patients with depression, data related to endocrine disorders in which hypercortisolemia exists do not point to receptor resistance as a major contributing factor. Junker (41) and Kontula et al. (42) demonstrated that neither in patients with Cushing's syndrome nor in those receiving high doses of synthetic steroids was there a change in lymphocyte, adrenal carcinoma, or pheochromocytoma glucocorticoid receptor number or affinity. There are mixed data related to lymphocyte glucocorticoid receptors in patients with major depression. Schlechte and Sherman (43) identified no significant differences in receptor

concentrations in 20 patients with depression when compared to 18 control subjects and the subgroup of DST nonsuppressors; however, Gormley et al. (44) were able to identify a significantly lower number of mononuclear cytoplasmic glucocorticoid receptors in 11 patients with major depression than in 14 control subjects.

Studies of peripheral glucocorticoid receptor sensitivity in lymphocytes may not reflect activity of glucocorticoid receptors in the CNS (45). Therefore, the studies by Schlechte and Sherman (43) and Gormley et al. (44), despite their inconsistencies, may not reflect the feedback activity of cortisol at the hypothalamus and pituitary. Basic studies of glucocorticoid receptor sensitivity would suggest that receptor downregulation should occur with increasing levels of glucocorticoid in media bathing receptor membranes (46). Variation in receptor activity, receptor modifying factors, cellular differentiation, and receptor concentration may however, influence in vivo receptor sensitivity.

An alternative to receptor resistance is that there is rather, an actual decrease in the number of receptors due to neurotoxicity from prolonged exposure to hypercortisolemia. Sapolsky et al. (47, 48) have demonstrated that extended glucocorticoid exposure selectively reduces hippocampal neurons, presumably through induction of a catabolically vulnerable state (49). Such neurotoxicity causes cell death in some areas while sparing others. This form of limbic system damage may help explain the self-perpetuating nature of the hypercortisolemia in depressed patients and implicate cortisol as a potential etiologic factor in the development of depression through its direct toxic effects on the "affective centers" in the limbic system. It does not, however, explain the initiating event for the hypercortisolemia in the first place.

Should glucocorticoid receptor resistance be invoked as the major reason for HPA axis abnormalities in patients with depression, cortisol nonsuppression after dexamethasone and hypercortisolemia are easily explained. However, one would not expect to find a blunted ACTH response to CRH (11, 12, 20–22, 50) or insulin-induced hypoglycemia (10). Rather, an accentuated response to these stimuli when baseline cortisol levels are controlled should be evident, since the pituitary would be very receptive to these releasing stimuli.

One way to estimate glucocorticoid receptor sensitivity (11) is to correlate basal cortisol with the basal or stimulated ACTH. According to this model, a negative correlation would be consistent with the hypothesis that the glucocorticoid receptors are sensitive to the feedback action of cortisol. A negative correlation with a greater ACTH-to-cortisol ratio would suggest relative glucocorticoid receptor insensitivity, while loss of the negative correlation would suggest relative hypersensitivity. (It should be noted that alteration in these ratios can also be the result of decreased glucocorticoid receptor affinity or number or can be a reflection of hypothalamic-pituitary hyperstimulation that overrides an otherwise normal adrenal-pituitary feedback mechanism.)

Several investigators have reported such an inverse relationship of the ACTH response after CRH challenge to basal cortisol in patients with major depression (11, 12, 21). Hermus et al. (51) have also identified a negative correlation in control subjects. An inverse relationship, however, has not been uniformly found after CRH challenge (22, 50), while recent work by our group suggests that basal cortisol is also not related to ACTH response during the insulin-induced hypoglycemia test in control subjects or depressed patients (10).

The reason for discrepancies among these studies is uncertain. The studies of Gold et al. (11) and Holsboer et al. (12, 21) were performed in the evening, while those by Amsterdam et al. (50) and Holsboer et al. (22) were performed during mid-afternoon. It is possible that basal evening cortisol levels are better predictors of feedback regulation. In fact, "resetting" of corticosteroid feedback sensitivity does occur during circadian ACTH-cortisol rhythms (52). Hermus et al. (51), however, performed their testing at 9:00 a.m., which suggests that diurnal variability may not be a major factor. While Hermus et al. (51) used 200 µg of CRH for their stimulation and the others used 100 µg (15, 25) or 1 µg/kg of body weight (11), all used concentrations that would be expected to give a maximal ACTH and cortisol response (53). Other obvious factors contributing to the differences between these results are not apparent. Regardless of the cause of the discrepancies, the results point to no glucocorticoid receptor insensitivity. At the very least, sensitivity would be equivalent to that expected in the general population. Hypersensitive glucocorticoid receptors in the absence of another factor influencing ACTH/cortisol production are unlikely, since that would result in a net decrease in serum and urinary cortisol—the opposite of that found in depressed patients.

Recent conflicting reports by Holsboer et al. (22, 54) and Gold et al. (55) regarding CRH testing in acute and recovered patients with depression deserve note. Gold et al. (55), using ovine CRH with evening administration, found a reversion toward normal of the blunted CRH responses in patients with major depression after successful treatment, while Holsboer et al. (22), also using ovine CRH with evening administration, found no such change. In a recent report of human CRH administration (54) in acute and recovered depressive patients, there was actually a decrement in ACTH and cortisol response with clinical improvement. Many factors could be involved in these conflicting findings, not the least of which is the small number of subjects involved in each project. Understanding ACTH and cortisol response to CRH administration in acute depression as a reflection of that seen in the recovered state will have to await further testing.

ADRENAL HYPERRESPONSE

Adrenal hyperactivity that occurs either autonomously or in response to increased circulating levels of

ACTH is also a potential source of DST nonsuppression (7, 8, 30). Autonomous adrenal hyperactivity is unlikely, given normal to high basal ACTH in patients with major depression (23–26), dexamethasone responsiveness (although with early escape) (31, 32, 35–39), and decreased, not absent, ACTH response to CRH in patients with depression (11, 12, 20–32, 50, 55). Patients with autonomous cortisol production from adrenal adenomas or carcinomas have low basal ACTH (56), insensitivity to dexamethasone (19, 56), and nonresponse to CRH (57, 58).

Several investigators (7–12, 30) have documented adrenal hyperresponsiveness to a given level of ACTH stimulation in patients with depression. This finding is true for both endogenous (9–12) and exogenous (7, 8, 30) stimulation with ACTH. Other findings related to HPA axis function in patients with depression are consistent with this as a potential contributing factor in the development of hypercortisolemia in depression.

A possible explanation for adrenal hyperactivity could be that there is increased enzyme activity in the adrenal gland, leading to the more rapid accumulation of cortisol. This possibility would be supported by the findings of Holsboer et al. (59, 60), which suggest increased post-DST 11-beta-hydroxylase activity in patients with depression. This enzyme controls the rate of conversion of 11-deoxycortisol to cortisol in the glucocorticoid pathway and the conversion of 11-deoxycorticosterone to corticosterone in the mineralocorticoid pathway. Although the hypothesis that there is increased enzyme activity is attractive, recent work in our laboratory suggests that the apparent increase in 11-beta-hydroxylase activity in depression is more related to DST nonsuppression than it is to a true increase in enzyme production (61, 62). Further work in this area is needed before a definitive answer is available.

Another possible and perhaps more likely reason for increased adrenal responsiveness to ACTH in patients with depression is that it is the natural result of adrenal hypertrophy due to chronic stimulation by endogenous ACTH. This finding is evident in patients with pituitary-dependent Cushing's disease (19) and is supported by the fact that both stress (63) and several days of stimulation with exogenous ACTH (64) can induce hypertrophy and hyperresponsiveness of the adrenal gland. Although patients with depression usually do not exhibit physical signs of chronic adrenal hyperstimulation, finding increased 24-hour ACTH secretion (23–26) and increased CSF CRH (27–29) during depression is consistent with this possibility.

Recent studies by Amsterdam et al. (65) and Dorovini-Zis and Zis (66) have suggested that adrenal size is increased in depressed patients compared to nondepressed populations. In the former study the comparison entailed the measurement of adrenal volume, as determined by computed tomography of the abdomen, in 16 depressed outpatients and 11 healthy volunteers. In the latter, adrenal weight was compared in patients

who died of violent suicide and in an age-matched control group who died suddenly from natural causes.

SUPRAHYPOPHYSEAL OVERACTIVITY

Increased pituitary stimulation from hypothalamic/limbic structures that overrides the feedback action of dexamethasone is an attractive consideration as the cause of DST nonsuppression (7–12). This consideration is supported by the blunted ACTH response to the ACTH secretagogue CRH (11, 12, 20–22, 50, 55) and to stress inducers such as insulin-induced hypoglycemia (10). That hyperstimulation is located central to the pituitary gland has been suggested by Gold et al. (11) in a comparative report of patients with Cushing's disease and patients with major depression. In that informative study patients with pituitary-dependent Cushing's disease demonstrated an augmented ACTH response to CRH, while patients with major depression had a blunted response. It is known that hypercortisolemia in patients with pituitary-dependent Cushing's disease is caused in most cases by autonomous ACTH production by pituitary microadenomas (56, 67). If this were the site of abnormality in patients with major depression, one would expect to see an augmented ACTH response similar to that seen in Cushing's disease patients. The reverse is the case.

Stimulation of the pituitary with chronic CRH administration causes downregulation of corticotroph receptors in the pituitary and results in a decrease of ACTH production in response to acute CRH administration (68). Since these basic research findings agree with the *in vivo* results of CRH stimulation in patients with major depression (11, 12, 20–22, 50, 55), it is reasonable to consider the possibility that CRH receptor downregulation due to chronic overproduction of endogenous CRH could contribute to the blunted ACTH response in this group.

Downregulation of pituitary CRH receptors is only one of the ways in which the pituitary adjusts to chronic CRH stimulation. Recent evidence shows that there not only is CRH receptor downregulation, but there is also a threefold increase in the number of pituitary corticotrophs (69). Data on patients with depression (10–12, 20–22, 50, 55) suggest that if chronic CRH overproduction does occur, CRH receptor downregulation overrides the effect of pituitary corticotroph hyperplasia.

Vasopressin is another hypothalamic peptide with trophic effects on ACTH production. Just as chronic hypersecretion of CRH can lead to CRH receptor downregulation, so also can chronic vasopressin administration downregulate vasopressin receptors (70). Findings by Meller et al. (9) are consistent with vasopressin receptor downregulation, although there was only a trend toward a reduction in ACTH response to acute arginine vasopressin administration. In the Meller et al. study it was argued that arginine vasopressin played a limited role as a regulatory neuropep-

tide involved in the ACTH and cortisol changes found in patients with depression, since there was no significant difference in ACTH response from control subjects. An alternative possibility is that there is also vasopressin receptor downregulation due to chronic hypersecretion of vasopressin. This leads to a blunted (or nearly so) ACTH response to acute vasopressin stimulation.

Comparison with results during vasopressin testing in patients with pituitary-dependent Cushing's disease supports the latter hypothesis. James et al. (71), Bethg et al. (72), and Krieger and Luria (73) demonstrate that patients with Cushing's disease had a comparably to significantly augmented cortisol response after administration of lysine or arginine vasopressin. Krieger and Luria (73) showed that this augmented cortisol response is likely to be the result of a concurrent exaggerated ACTH response. Augmented ACTH and cortisol activity would be expected in Cushing's disease patients, since the autonomously functioning ACTH-producing corticotrophs are primed to hyperrespond to otherwise quiescent hypothalamic trophic neuropeptides. The response in patients with depression tends to be in the opposite direction and is more consistent with hyperstimulation central to the pituitary.

Lopez et al. (10) have shown that there is a decrease in ACTH response to insulin-induced hypoglycemia in patients with major depression when compared to control subjects. In the animal model a decreased ACTH response to hypoglycemia is presumably mediated through alterations in vasopressin levels in the presence of the necessary co-factor CRH (74). If a similar mechanism for the ACTH response to hypoglycemic stress is also present in humans, a blunted but not absent ACTH response is exactly what would be expected, since both CRH and arginine vasopressin may independently result in a blunted ACTH response.

Patients with Cushing's disease represent a group in which there is also a decreased ACTH response to insulin-induced hypoglycemia (73). In these patients the blunted response is thought to be largely due to the substantial feedback inhibition of ACTH and cortisol on CRH/arginine vasopressin production. This hypothesis is supported by studies in which acute vasopressin administration resulted in increased ACTH or cortisol responses, whereas insulin administered to the same patients resulted in a lack of response of either ACTH or cortisol (72, 73). Patients with Cushing's disease are able to mount a very limited ACTH response after insulin administration. This leads to the well-defined blunted-to-absent cortisol response (75), which in years past has been suggested as one way to distinguish patients with depression from those with Cushing's disease (19).

It is impossible to tell whether the ACTH blunting in depressed patients after insulin-induced hypoglycemia is influenced to a greater extent by glucocorticoid feedback from elevated circulating cortisol or a decreased pituitary response to adequately stimulated endogenous arginine vasopressin or CRH. Since patients with

depression have elevated CSF CRH levels when compared to control subjects (27, 28), and there is a trend toward such in DST nonsuppressors (29), while patients with Cushing's disease have decreased levels of CSF CRH (76), it is less likely that the blunted ACTH response after insulin-induced hypoglycemia in depressed patients is due purely to feedback inhibition. If feedback inhibition were a prominent control mechanism for ACTH and cortisol secretion in depression, then it would also be expected in the basal state. CSF CRH levels and basal plasma ACTH and cortisol levels speak against this as a major control factor. The data regarding CSF arginine vasopressin levels in patients with depression (77) suggest that vasopressin is decreased when compared to a control population, a finding opposite to what we would expect from the results of our data.

Coupling a trend toward blunted ACTH response to arginine vasopressin with the blunted ACTH response to CRH, one can theorize that a supra-hypothalamic stimulus or autonomous secretion of the parvocellular neurons of the paraventricular nucleus leads to a chronic increase in the production of arginine vasopressin/CRH. ACTH and cortisol hypersecretion occur as a natural consequence in patients with depression. This theory is consistent with other HPA abnormalities found in patients with depression. Although it is impossible to tell whether feedback inhibition plays a cardinal role in the decreased ACTH response to insulin-induced hypoglycemia as is likely in pituitary-dependent Cushing's disease, the findings of Lopez et al. (10) on the insulin-induced hypoglycemia test also fit into this unified package.

The above discussion has focused on the pathophysiology of cortisol abnormalities in patients with depression and has suggested that hypothesis four in our first paragraph comes closest to explaining existing HPA axis findings in depression. However, it does not address the etiologic relationship these changes have to the depressive syndrome. Although current evidence suggests that there is an abnormality in the hypothalamic/limbic driving force of the pituitary-adrenal axis that may be mediated by CRH or vasopressin, this abnormality may be only partially related to the behavioral syndrome.

The etiology of HPA axis changes in patients with major depression could also be epiphenomena, i.e., associated with other aspects of the depression rather than the depression itself. Stress, for instance, has always been considered a potential interfering variable (78). Although stress is a logical candidate to cause the HPA axis abnormalities identified in patients with depression, there are few studies of psychological stress which support this as a possibility (79). Psychological stress, by itself, has relatively little demonstrable effect on ACTH and cortisol secretion, while chronic stress tends to readjust possible changes in ACTH and cortisol production toward normal with time.

Weight loss could also be a factor in inducing cortisol changes in depression (80–84). As an interfering

variable, this is less easy to dismiss. Several studies of major depression have suggested that at least some of the variance in HPA axis hypersecretion could be explained by appetite disturbance with weight loss (82, 83, 85). Findings in other studies, however, would not agree (80, 86, 87). Since patients with anorexia nervosa, a condition defined by weight loss, also show a high rate of DST nonsuppression (88), as well as ACTH blunting after CRH administration (89), weight loss as a factor in HPA axis changes in major depression has to be further considered.

The relationship of increased HPA axis abnormalities to age in depressed patients is interesting as well (90–93). Older patients with major depression are more likely to be DST nonsuppressors (90–93). Although a study by Oxenkrug et al. (94) indicates that such age-related changes may also be present in control subjects, there are several studies which suggest that this may not be the case (92, 95). When one looks at urinary-free cortisol excretion as an index of HPA axis dysfunction, age is also directly related to cortisol production in depressed patients (96). However, similar findings have not been demonstrated with control subjects (97).

A final intriguing hypothesis is that HPA axis abnormalities in patients with depression are in some way related to the development of depression (98). Even if this is the case, it is not certain that the proposed central hypothalamic/limbic defect would be the cause of the symptoms, since hypercortisolemia itself could be more closely related to the development of symptoms. The work of Sapolsky et al. (47, 48), in which limbic system neurons show a susceptibility to toxic effects of glucocorticoids, supports this hypothesis; and, after all, patients with primary adrenal and pituitary-dependent Cushing's disease have a high yet equal prevalence of depressive symptoms, and these symptoms subside with treatment of the hypercortisolemia alone (98).

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RDC Alcoholism in Patients With Major Affective Syndromes: Two-Year Course

Deborah S. Hasin, Ph.D., Jean Endicott, Ph.D., and Martin B. Keller, M.D.

The authors examined the 2-year course of alcoholism as defined by Research Diagnostic Criteria (RDC) in 127 newly admitted patients with major affective syndromes and concurrent alcoholism at intake. The cumulative probability of remission (at least 6 months free of alcohol problems) in these patients was 0.67. Many of the remissions began within a few weeks of intake; the remaining were distributed over the follow-up period. Of the patients without remissions, 17% died, half by suicide. Diagnoses of schizoaffective disorder, indicators of alcohol dependence, and previous chronicity of alcohol problems predicted poor outcome of alcoholism, but none of these variables predicted subsequent relapse.

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We have shown previously that many patients with affective syndromes abuse alcohol during episodes which bring them into treatment (1). Much literature exists on the course of alcoholism in patients treated in alcohol-identified settings, and epidemiologists also have studied persistence of alcohol problems in the community (2). However, the prospective study of concurrent alcoholism in psychiatric patients presenting primarily for treatment of other mental disorders appears to be relatively unresearched. In this pa-

per, we describe the patterns and predictors of remission and relapse of alcoholism diagnosed according to Research Diagnostic Criteria (RDC) (3) over 2 years of follow-up in patients concurrently treated for major affective syndromes. Specifically, we examine 1) the time to remission of alcoholism, 2) predictors of remission, 3) time to relapse in those who experienced a remission, and 4) predictors of relapse within the period at risk.

METHOD

The patients were a subset of the 955 participants in the NIMH Collaborative Study on the Psychobiology of Depression (Clinical Studies Section). Details of this study are described elsewhere (3–5). Briefly, subjects meeting RDC for major affective syndromes assessed with the Schedule for Affective Disorders and Schizophrenia (SADS) (4) were recruited from five medical school treatment settings. Of the initial sample, 135 patients received additional RDC diagnoses of probable or definite current alcoholism; 127 (94.1%) of these patients participated in the follow-up study.

All 127 patients were Caucasian, 51 (40.2%) were women, 39 (30.7%) were married, and 30 (23.6%) had never been married. Eight-six (67.7%) were under 40 years of age, and 96 (75.6%) had household incomes under \$22,000. Thirty-four (26.8%) of the patients were from Iowa City, 30 (23.6%) were from Boston, 41 (32.3%) were from St. Louis, and 22 (17.3%) were from New York or Chicago. Only 15 (11.8%) were outpatients. Six (4.7%) of the patients had schizoaffective disorder, manic or depressed type; 17 (13.4%) had bipolar I disorder; 10 (7.9%) had bipolar II disorder; and 94 (74.0%) had major depressive disorder.

The RDC intentionally provide a low-threshold, inclusive definition of “alcoholism.” Therefore, subjects

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an meet RDC for this disorder with milder drinking problems than would ordinarily be seen in alcoholism treatment settings. In this sample, some patients had only the minimum number of symptoms necessary to receive an RDC diagnosis of probable alcoholism and therefore experienced very low levels of alcohol difficulties. Others presented with a picture of considerable clinical severity. Out of a total of 18 possible RDC alcohol symptoms, the mean \pm SD number shown by the patients in this sample was 7.04 ± 3.77 . For comparative purposes, we note that the mean number of such symptoms in a random sample of 123 alcohol rehabilitation patients interviewed at about the same time was 9.88 ± 3.16 (6). For the purposes of this study, using the RDC alcohol diagnosis as an inclusion criterion allowed us the advantage of examining aspects of alcohol-related severity over a broad range.

Subjects were evaluated with the SADS and RDC as soon as possible after either admission to the hospital or their first outpatient appointment. These evaluations included information obtained from clinical staff, significant others, and previous medical records. All patients gave informed consent after the study had been explained.

Follow-up information for this study was obtained every 6 months by using the Longitudinal Interval Follow-Up Evaluation (5), which provides a format for separately charting the severity of multiple specific mental disorders (including RDC alcoholism) on a weekly basis. Clinical interviewers administering the Longitudinal Interval Follow-Up Evaluation probed for major changes in the patients' conditions during the preceding 6 months. When changes occurred, interviewers probed for the week in the study when the change occurred, exploring the relationship of these changes to holidays and other events if necessary.

In the Longitudinal Interval Follow-Up Evaluation, alcoholism was rated on a 3-point scale. A score of 1 indicated that the patient met criteria for a definite diagnosis, a score of 2 indicated some evidence of alcohol problems but not enough to meet full criteria for a diagnosis, and a score of 3 indicated no evidence of any RDC symptoms of alcoholism. Abstinence from alcohol was not required for the score of 3. However, raters explored very carefully for any RDC alcoholism symptoms when interviewing current drinkers with previous alcohol diagnoses.

For the analyses reported here, we defined "remission" from RDC alcoholism as 26 weeks or more with no evidence of any RDC alcohol symptoms. We required at least 26 weeks in order to study a change with some degree of stability in a condition that is often episodic. Relapse was defined as any occurrence of RDC alcohol symptoms following 26 weeks of remission as defined. The onset date of remission was week 1 of the 26 or more weeks required. The starting date of a relapse was the first week in which any alcohol symptoms occurred following 26 weeks of remission.

The potential predictors of 2-year course, evaluated

at intake, can be grouped as demographic, clinical-diagnostic, and alcohol specific. Since community surveys show that alcohol problems of young adults and women are more likely to remit than those of older individuals and men (2, 7, 8), we predicted that older subjects and male subjects would experience poorer outcome. We included living situation (alone versus with others) among the demographic variables on the grounds that lack of exposure to the social disapproval of others in the home might pose a risk factor for patients living alone. Literature on the effect of income has been mixed (9); we included income for descriptive purposes.

The clinical-diagnostic predictors included subtypes of affective disorder, cycling between poles during the index episode of affective disorder, a global measure of severity, and a diagnosis of antisocial personality disorder. Reich et al. (10) showed that heavy drinking was associated with manic phases of bipolar illness, so we predicted that patients with bipolar disorders would have worse outcomes. We did not have a specific prediction about schizoaffective disorder. Cycling between affective poles during the intake episode predicted very poor outcome of affective disorders (11) and was therefore expected to predict poor outcome of the alcoholism as well. We expected that poorer functioning or severity of illness as measured by the Global Assessment Scale (12) would predict poorer outcome of alcohol problems. Rounsaville et al. (13) showed that broadly defined antisocial personality disorder is prognostic of poor outcome for alcoholism, so patients with additional diagnoses of antisocial personality disorder were expected to experience poorer outcome of their alcoholism.

We included three alcohol-specific predictors. One concerned past chronicity. This often predicts future chronicity, so we included a variable representing brief (less than 6 months) or chronic duration of RDC alcoholism before entry into the study.

We derived the other two alcohol-specific predictors from concepts related to the Edwards-Gross alcohol dependence syndrome (14). This syndrome includes such symptoms as tolerance, withdrawal, drinking to relieve or avoid withdrawal, drinking increasingly unaffected by ordinary social conventions regarding appropriate drinking behavior, and the feeling of compulsion or impaired control (a key feature). The alcohol dependence syndrome was proposed as a continuous dimension of alcohol problems distinct from drinking-related social or occupational impairment (14). *DSM-III-R* and *ICD-10* draw more heavily on this concept of alcohol dependence than did earlier diagnostic systems (*DSM-III*, 3, 15). Although alcohol-related social and/or occupational problems have been shown to be somewhat transient in the general U.S. population (16), the alcohol dependence syndrome was conceptualized as prognostic of continued difficulties with drinking (17). Rounsaville et al. (13) showed that the severity of the alcohol dependence syndrome predicted poor outcome in treated alcohol-

ics. Therefore, we wished to distinguish indicators of the alcohol dependence syndrome from social-occupational problems and evaluate each as predictors of outcome.

Seven RDC items cover aspects of the alcohol dependence syndrome (feeling one can't stop, morning drinking, repeated benders, shakes, delirium tremens, hallucinations after drinking, and withdrawal seizures). We constructed a 7-item summation scale to measure the severity of the alcohol dependence syndrome with these dichotomous items. The scale had acceptably good internal consistency ($\alpha=0.70$ as determined with the KR-20 formulation of alpha, the standard formula for internal consistency with dichotomous items [18]). Items covering alcohol-related social-occupational problems from the SADS were treated similarly (others objecting, trouble with family or friends, divorce, job problems, losing a job, repeated violent behavior, driving problems, trouble with police) and also formed an acceptably reliable scale ($\alpha=0.68$).

Some patients died or were lost to follow-up without remission, and others had not remitted at all by the end of the 2-year follow-up period. Therefore, we used survival analyses. We obtained product-limit estimates of the probability of recovery for each week of the follow-up period. We found that site (potentially a multicategory control variable) was not significantly associated with time to recovery using Gehan's generalized Wilcoxon tests (19), so we did not control for this in further analyses. We tested the univariate association of the predictor variables with time to recovery using Kalbfleisch and Prentice's extension of generalized Wilcoxon tests (20). Among patients with remissions, we used the same procedures for testing time to relapse. The Cox proportional hazards model to simultaneously examine the effects of multiple predictors of time to an event assumes that hazard ratios between groups are consistent over time. Plots of $\log(-\log)$ survival estimates by subgroup showed that this assumption was violated for several predictor variables. Therefore, we used simultaneous logistic regression to test whether the predictor variables conjointly gave approximately the same results as the univariate tests, regressing the predictor variables on 1) remission by 2 years (yes or no) and 2) relapse among those with remissions.

RESULTS

We followed 107 (84.3%) of the patients for the entire 2-year period. Eight patients were followed for a shorter period of time (range=2–91 weeks) because they died, including five who were followed for less than 6 months. The remaining 12 were either lost to follow-up or refused further participation before the end of the study period (range=26–78 weeks).

Over the 2 years of follow-up for this sample, the cumulative probability of remission from RDC alco-

FIGURE 1. Cumulative Proportion of Patients With Concurrent Affective Disorders Who Recovered From Index Episode of RDC Alcoholism (N=127)

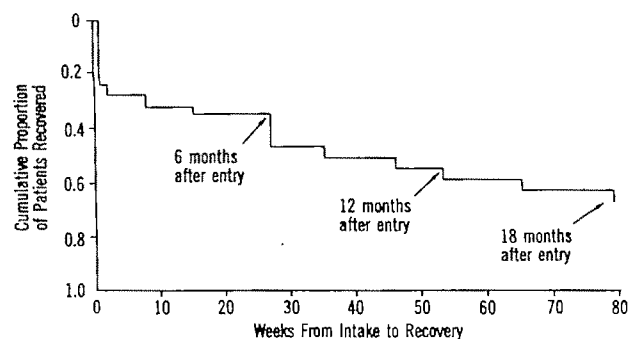


TABLE 1. Predictors of Time to Remission of RDC Alcoholism in 127 Patients With Concurrent Affective Disorders^a

Predictor	χ^2 (df=1)
Age	1.02
Sex	0.55
Living alone	0.00
Income	0.95
Diagnosis	
Schizoaffective disorder	4.08 ^b
Bipolar I	0.21
Bipolar II	5.48 ^c
Antisocial personality	0.21
Global Assessment Scale score	0.03
Alcoholism longer than 6 months	10.04 ^d
Alcohol dependence indicators	6.41 ^e
Social-occupational problems	0.63

^aRemission was defined as 26 weeks or more with no evidence of any RDC alcoholism symptoms. Predictors were determined with univariate survival analysis.

^bSignificantly associated with poorer outcome ($p<0.05$).

^cSignificantly associated with better outcome ($p<0.05$).

^dSignificantly associated with poorer outcome ($p<0.01$).

^eMore indicators significantly associated with poorer outcome ($p<0.05$).

holism for at least 6 months was 0.67. Of the 79 patients who remitted, the cumulative probability of relapse by the 2-year point was 0.29. None of the patients with remissions (either sustained or not) had died by the end of the 2 years. Of the 48 patients without remissions, eight (16.7%) died; four by suicide. Two of the others died while heavily intoxicated (one of exposure, one from aspirating vomit). One was fatally shot in a bar during a holdup, and the last died of cancer.

Figure 1 shows the product-limit estimates of the probability of remission, by week, during the 2 years. As shown, many remissions occurred during the first several weeks. By 12 weeks, the cumulative probability of remission was 0.34. However, patients continued to remit throughout the time in which subjects could cease experiencing drinking problems and remain in this state for 26 weeks (week 78). At 6 months, the

TABLE 2. Cumulative Probability of Remission of RDC Alcoholism Subgroups of Patients With Concurrent Affective Disorders^a

Subgroup	Cumulative Probability of Remission			
	Week 12	Week 26	Week 52	Week 104
Schizoaffective disorder (N=6)	0.17	0.17	0.17	0.17
Bipolar II disorder (N=10)	0.70	0.70	0.85	0.85
Alcohol problems for less than 6 months (N=24)	0.63	0.71	0.76	0.81
Three or more alcohol dependence indicators (N=43)	0.23	0.26	0.39	0.50
Total (N=127)	0.34	0.37	0.52	0.67

^aProbability of remission was determined by using product-limit estimates. Only subgroups that showed statistically significant differences are listed.

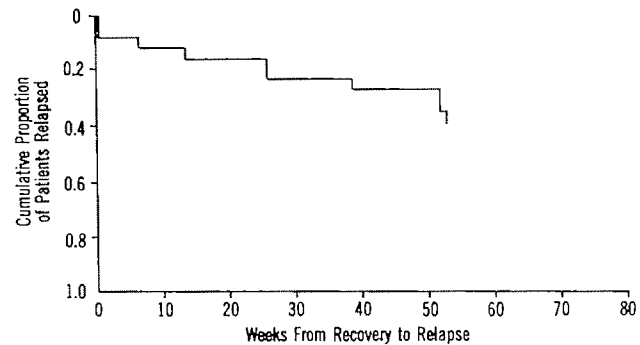
Cumulative probability of remission was 0.37; at 1 year, 0.52; and at 2 years, 0.67.

Table 1 shows the results of the tests for the association of the predictor variables with time to remission from alcoholism. Neither age, gender, living alone, nor household income had a significant relationship to time to remission. In contrast, even with only six patients with schizoaffective disorder and consequently little statistical power, schizoaffective disorder was significantly related to longer time to remission. As shown in table 2, the cumulative probability of remission for the patients with schizoaffective disorder by the end of follow-up was only 0.17. RDC Bipolar II also rare, N=10) was also significantly related to remission, but in the opposite direction; the cumulative probability of remission for subjects with this subtype was 0.85 by the 2-year point. No other clinical-diagnostic variable was significantly associated with time to relapse. Table 2 shows the cumulative probabilities of remission for the subgroups that showed statistically significant differences.

In this sample, 24 (18.9%) of the subjects experienced only brief alcohol problems (6 months or less) before entry into the study. As shown in table 2, we found that brief duration was associated with earlier remission. We also found that higher scores on the dependence scale were associated with poorer outcome. However, the social-occupational dimension of alcohol-related problems was not significantly associated with time to remission, even though subjects had scores throughout the entire range of severity on this scale, from none of these problems (seven patients, or 5.5%) to seven or eight of them (10 patients, or 7.9%).

As already noted, logistic regression was used as a partial check on whether the results of the univariate tests would hold up in a multivariate analysis. Regressing remission (yes or no) on the independent variables listed in table 1 produced results similar to those obtained with the individual tests, although some statistically significant predictors in the Wilcoxon tests just missed statistical significance in the logistic regression (schizoaffective disorder, $\chi^2=5.66$, n.s.; alcohol dependence indicators, $\chi^2=5.24$, $p<0.05$; bipolar II disorder, $\chi^2=3.17$, n.s.; alcoholism longer than 6 months, $\chi^2=2.81$, $p<0.10$) (all values for $df=1$). Since we did not find major decreases in significance levels in the multivariate test, we concluded that our univariate survival analyses of remission were not spurious due to confounding or redundancy of variables.

FIGURE 2. Cumulative Proportion of Patients With Concurrent Affective Disorders Who Recovered From Index Episode of RDC Alcoholism But Then Relapsed (N=79)



der, $\chi^2=3.17$, n.s.; alcoholism longer than 6 months, $\chi^2=2.81$, $p<0.10$) (all values for $df=1$). Since we did not find major decreases in significance levels in the multivariate test, we concluded that our univariate survival analyses of remission were not spurious due to confounding or redundancy of variables.

Since alcoholism treatment was not randomly assigned to the patients in this study, we could not assess the influence that treatment had on outcome, although there was a slight (nonsignificant) tendency for patients with worse outcome to have had treatment specifically for alcohol problems during the follow-up period. Six (7.6%) of the 79 patients with a remission were treated in inpatient detoxification, nine (11.4%) received treatment in alcohol rehabilitation, 15 (19.0%) attended Alcoholics Anonymous (AA) during the 2 years, and 15 (19.0%) took disulfiram. Of the 48 patients without a remission, 11 (22.9%) had inpatient detoxification, seven (14.6%) were treated in alcohol rehabilitation, eight (16.7%) attended AA, and 10 (20.8%) took disulfiram.

We next considered relapse. Figure 2 presents the product-limit estimates of the probability, by week, of relapse after 26 weeks of remission. The times at risk for relapse were quite variable because subjects who began remissions later had less time at risk for subsequent relapse. As shown, relapse was more evenly spread over time than initial remission. No variable tested as a predictor of remission was significantly associated with relapse.

DISCUSSION

These data illustrate that the outcome of problem drinking in patients with major affective syndromes is quite variable. A number of the patients in this sample ceased experiencing alcohol problems almost immediately after entry into the study. Others took longer to remit. About two-thirds of those whose alcohol problems remitted maintained this status, while others relapsed. A high proportion of subjects who did not remit died, consistent with the literature indicating

increased mortality among those with alcohol problems (21–23).

Previously (1), we found that subtype of affective syndrome did not predict concurrent alcohol problems. However, certain subtypes do seem to predict outcome once alcohol problems have commenced. Patients with schizoaffective disorder were unlikely to remit from drinking problems, and the follow-up case narratives of these patients indicated that they generally had a very hard time and were difficult to treat. Bipolar I disorder was not associated with time to remission, perhaps because manic episodes during the follow-up were treated quickly enough to prevent problems from mania-related drinking. We are unsure how to explain the finding that patients with bipolar II disorder had a significantly shorter time to remission.

We did not find the predicted relationship of antisocial personality disorder with poor outcome. Woody et al. (24) found that opiate addicts with major depression and antisocial personality disorder improved after treatment, but opiate addicts with antisocial personality disorder and no depressive disorder showed little improvement. Rounsaville et al. (13) did not differentiate their antisocial alcoholic subjects into those with and those without major depression. Perhaps depression in alcoholic antisocial individuals (such as those included in this report) indicates a difference in personality structure; such individuals might have a greater capacity to engage in treatment and improve than do individuals with antisocial personality disorder who do not become depressed.

Defining "remission" or "recovery" from alcoholism is difficult and somewhat controversial. Some may find our definition too rigid, while others may object that we did not require complete abstinence from alcohol. We would have preferred to analyze outcome on many dimensions of alcohol problems, but such information was not available. Given the scarcity of information on our topic, the analyses seemed warranted with the data at hand. Future research on the outcome of alcohol problems in patients with mental disorders would be improved by separate measurement and analyses of many dimensions of alcohol dependence and related difficulties.

An additional measurement issue is the validity of self-report information on alcohol consumption and problems. Information was corroborated at times from other informants, but not routinely. However, family reports often do not reveal alcohol problems that subjects themselves are willing to discuss with research interviewers (25). Some of our subjects probably minimized their difficulties with drinking, but they were the only ones who could report on the more subjective aspects of their drinking experiences.

Also, patients were probably not completely accurate in the dating of remission and relapse. Some patients may have remembered exactly when their remissions began (for instance, AA members who could date anniversaries of abstinence), but this was not such a clearly demarcated event for others. Nevertheless, us-

ing subjects' estimates of the timing of a remission probably provides more information than simply noting remission as a yes-or-no phenomenon at some point in time. Even if subjects miscalculated by a month or two, the fact that the information was reviewed with subjects every 6 months served to locate approximately when the remission took place.

The criteria for the Edwards-Gross alcohol dependence syndrome (14), introduced in 1976, now form much of the basis for the alcohol dependence criteria of both *DSM-III-R* and *ICD-10*. Although research is needed on the psychometric properties of these criteria, the fact that dependence indicators predicted outcome while social problems did not argues for the differentiation of at least these two dimensions of alcohol use disorders. A possible implication of the finding is that multiple indicators of the alcohol dependence syndrome can be taken as evidence of a drinking problem for which the goal of abstinence may be an especially important part of the treatment.

We were unable to identify significant predictors of relapse among the patients whose alcohol problems remitted. However, the time at risk for a relapse was much shorter than the time in which patients could show a remission. Data will soon be available on these patients for an additional 3 years, allowing more complete analysis of relapse over an extended period of time.

Our results were obtained for patients with particular types of mental disorders, and generalizability to patients with other disorders is not known. Given the high rates of comorbidity of alcoholism and various mental disorders, this is an area in which more research is needed. As information becomes increasingly available on these issues, clinicians may be more likely to address such problems in their patients, improving the chances of a good treatment outcome for all concurrent disorders.

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Clinical Differentiation Between Lethal Catatonia and Neuroleptic Malignant Syndrome

Edgar Castillo, M.D., Robert T. Rubin, M.D., Ph.D., and Edith Holsboer-Trachsler, M.D.

Lethal catatonia, a syndrome described several decades before the advent of neuroleptic drugs, has been regarded by many investigators as clinically similar to, and perhaps indistinguishable from, neuroleptic malignant syndrome. However, published case reports of the two syndromes indicate differences in mode of onset, signs and symptoms, and outcome. Lethal catatonia often begins with extreme psychotic excitement, which, if persistent, can lead to fever, exhaustion, and death. Neuroleptic malignant syndrome begins with severe extrapyramidally induced muscle rigidity. Because lethal catatonia often requires neuroleptic treatment and neuroleptic malignant syndrome necessitates immediate cessation of neuroleptics, their early clinical differentiation is important.

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Three decades of experience with neuroleptics have led researchers to conclude that this class of medications can produce substantial clinical side effects (1-4). One of the most severe, the neuroleptic malignant syndrome, has been the focus of increasing attention in case reports and reviews over the last several years (5-17).

Neuroleptic malignant syndrome affects patients of all ages who have a broad range of psychiatric disorders (10, 15-17). More than 20 different neuroleptics have been associated with neuroleptic malignant syndrome (16, 18). Symptoms appear within the first few days of neuroleptic administration and develop quickly into a syndrome that includes muscle hypertonicity and rigidity, persistent autonomic instability, altered consciousness, and fever (5, 7, 9, 10, 13-15, 17, 18). The mortality rate for patients with the full syndrome has been estimated to be as high as 30% (19, 20).

Received Sept. 28, 1987; revision received June 27, 1988; accepted Sept. 9, 1988. From the Department of Psychiatry, Harbor-UCLA Medical Center, and the Department of Psychiatry, University of Zürich, Switzerland. Address reprint requests to Dr. Rubin, Department of Psychiatry, Harbor-UCLA Medical Center, Torrance, CA 90509.

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The need for prompt and careful recognition of this potentially life-threatening illness is clear. However early detection is not easy, especially if the full syndrome is not present or if the signs are obscured by concomitant medical or organic brain disease (1, 5, 10, 13-15). One of the possibilities that needs to be considered in the differential diagnosis of neuroleptic malignant syndrome is so-called "lethal catatonia," an acute and progressive mental excitement with fever and continuous motor activity which often results in exhaustion and death (5, 6, 8, 9, 13, 14, 16, 21, 22).

Several reports have fostered the belief that lethal catatonia is clinically indistinguishable from neuroleptic malignant syndrome, and some investigators have suggested a common pathophysiological mechanism (8, 21-27). However, at present no general neurochemical theory can explain all the symptoms of these two disorders. Their differential diagnosis is important because of treatment considerations: For lethal catatonia, neuroleptic medication may be indicated (28-30), whereas in the management of neuroleptic malignant syndrome, neuroleptic medication must be stopped immediately (5, 7-14, 16, 17). The purpose of this report is to derive, from a literature review, a clinical differentiation of lethal catatonia from neuroleptic malignant syndrome, as an aid to clinicians in the management of these two syndromes.

HISTORICAL BACKGROUND

Kahlbaum, in 1874, identified catatonia as a symptom complex characterized by negativism, catalepsy, mutism, stereotypy, posturing, muscular rigidity, and verbigeration (31). He observed that some of his patients alternated between catatonic stupor and excitement. Kraepelin and Bleuler (32, 33) both included catatonic symptoms in their descriptions of dementia praecox and schizophrenia, respectively, but they were cognizant that Kahlbaum's catatonic symptom complex also could occur in other diseases. Many subsequent studies have confirmed the fact that catatonic morbid phenomena are indeed a group of signs and symptoms—a syndrome that varies greatly in onset, intensity, severity, and outcome (34-37).

Catatonia may occur as the defining characteristic of a psychiatric disorder (34, *DSM-III*), as a secondary

development in the context of other psychiatric illness (34–37, 38), or as an accompaniment to various medical conditions (34–36). It has different appearances at different stages in its course (31, 39). Current conceptions about catatonia continue to be based primarily on empirically derived groups of clinical observations rather than on an understanding of pathophysiological mechanisms.

Lethal Catatonia

The term “lethal catatonia” is only one among several that have been used in reference to a rather well-circumscribed group of signs and symptoms which, because of its severity and lethality, represents one extreme of the catatonic spectrum (40). Over the past several decades it has received various labels, including acute catatonic excitement (41), Bell’s mania (42), acute essential psychosis (43), psychotic exhaustion syndrome (44), Scheid’s cyanotic syndrome (45), acute pernicious psychosis (46), and delirium acutum (47).

In 1934, Stauder (40) published detailed observations of 27 cases, which became the definitive study of the syndrome that he called lethal catatonia. The cases were mostly young people, in the age range of 18 to 26 years, who had no significant premorbid psychological or physical disturbances. Stauder observed the acute onset of a severe form of psychomotor agitation that he called “elementary catatonic excitement.” Various degrees of clouding of consciousness and a strong tendency toward violent and self-destructive acts also were present. Another prominent finding was acrocyanosis, which occurred before or at the onset of the motor excitement. As the excitement persisted, a catatonic state of cramped posture and extremely tense muscles appeared, during which the patients still periodically continued to attempt to harm themselves or to climb out of bed. This lasted until they were physically exhausted and ultimately died. The duration of the entire episode was between 4 and 14 days.

Stauder’s findings have been confirmed by many other investigators (30, 41, 43–52). All have found it remarkable that autopsies of these patients revealed no clues as to etiology and failed to explain the cause of death, other than exhaustion.

Clinical Differences Between Lethal Catatonia and Neuroleptic Malignant Syndrome

A careful review of the case reports of lethal catatonia and other similar cases indicates that a clinical distinction from neuroleptic malignant syndrome is possible. A useful approach is to conceptualize lethal catatonia as an exhaustion syndrome, caused and maintained by relentless psychomotor excitement, several days to weeks in duration, which results in alterations in autonomic function (41, 43, 44, 48–50, 52). These alterations include fever, profuse perspiration, and rapid pulse, which, coupled with patients’ refusal to eat or drink, lead to progressive and rapid weight

loss, dehydration, hypotension, and general deterioration. As the psychomotor excitement continues, the hallucinatory and delusional components of the catatonic psychosis become intermixed with the resulting cachexia, organic-like delirium, convulsions, and coma.

In its final stage, lethal catatonia resembles almost any near-death acute confusional state of a toxic, metabolic, cardiovascular, or other organic etiology (40, 44–46, 50, 52). Thus, it is understandable that at this stage it might be confused with a number of other diseases, including neuroleptic malignant syndrome. However, careful scrutiny reveals that the clinical picture and course is not typical of neuroleptic malignant syndrome, either in its early stages or when the full syndrome is present.

Table 1 outlines the clinical distinctions between the two syndromes. Table 1, although divided into stages for illustrative purposes, is not meant to reflect a sharply defined sequence of events. Indeed, there is variability of signs and symptoms in both disorders and overlap in the timing of their appearance, but the division of the syndromes into clinical stages helps to emphasize the sequence of symptom appearance as well as the clinical differences between the two syndromes. The following two abridged case reports have been chosen as examples of these syndromes.

Case 1: lethal catatonia (from reference 40). A 25-year-old man, whose sister had died during a period of catatonic excitement, was in good health until he began talking senselessly one day. The next day he was confused and unable to work. The third day he was in severe psychomotor excitement, was aggressive toward his family, and wanted to jump out of the window. He was admitted to the hospital, and during the first few hours, he stated that he was afraid of being tortured and that he knew the torture instruments were already being prepared. He accused the staff of preventing him from entering a monastery and of being guilty against the mother of God. His statements were only partly coherent, and he denied that he was hallucinating. Because of severe excitement he was placed in a continuous water bath. Despite scopolamine and laudanum injections, he did not sleep at all. The following afternoon he was severely excited, attacking other patients and anyone who came near. The hematomas on his body, which were noted at admission, became bigger and turned yellow. His fingers and feet were cyanotic.

During his second night in the hospital, he slept for a few hours after taking medication, but he became excited again and his consciousness was clouded. His psychomotor excitement alternated between wild falling to the ground and short, quieter periods during which he grimaced wildly and fought when someone came near. Toward evening, he appeared calmer but weaker and spent that night and the next day in bed, but he again became excited and tense, banging his head into the pillows, tearing away his clothes, and thrashing about. During short intervals of negativistic stupor, he took some nourishment. The next morning the rigidity had changed back to a wild agitation; he was crying, biting, and falling to the ground and his face was bleeding. He jumped out of the water bath and did not respond to hyoscyamine injections.

On the eighth day in the hospital, the patient was so ex-

TABLE 1. Clinical Differences Between Lethal Catatonia and Neuroleptic Malignant Syndrome

Stage	Lethal Catatonia	Neuroleptic Malignant Syndrome
Onset	Prodrome lasting 2 weeks to 2 months, consisting of behavioral and personality changes or frank schizophrenic symptoms (21, 40, 49) Possible acute onset with no prodrome (41, 44, 45)	Period of prior neuroleptic exposure can be hours to months (10, 13, 17, 18, 20) Develops rapidly over a few hours to days (5, 7, 8, 13) No prodromal phase has been described (10, 13, 18, 20)
Initial symptoms	Excitement, intense anxiety, and restlessness lasting a few days (21, 40, 44, 49) Possible self-destructive or assaultive behavior (21, 40, 44, 49) Hallucinatory experiences and delusional thinking usually present (40, 44–47, 49, 51) Possible fever, tachycardia, and acrocyanosis (40, 45, 50) Sudden death may occur (44, 48, 51)	Tremors and dyskinesias are early signs (15) Muscle hypertonicity described as "lead pipe" or "plastic" rigidity (5, 7, 10, 14–17, 24) Severe excitement and intense anxiety are not major features (5, 7, 13–16, 18) Autonomic instability with tachycardia, labile hypertension, and possible diaphoresis (7, 15, 17) Fever may not be present initially (10, 18) Acrocyanosis has not been described (5, 7, 10, 13–16, 18) May occur in nonpsychotic patients treated with neuroleptics (7, 9, 13, 14, 16) No deaths reported during early phase
Full syndrome	Continued increasing excitement with wild agitation and violent, destructive behavior, lasting 3–15 days, and possible choreiform movements (14, 41, 44, 49) Mutism, rigidity, and/or stupor may alternate with excitement (40, 52) Refusal of food and fluids (40, 43, 44, 48) Increasing and fluctuating fever, rapid and weak pulse, profuse, clammy perspiration, hypotension (44, 48, 49, 52)	Appearance of most major symptoms (severe muscle rigidity, persistent autonomic instability, fever) usually occurs after 2–9 days (10, 15–17) Possible agitation, confusion, and clouding of consciousness (7, 9, 11)
Final stage	Cachexia, convulsions, delirium, coma, exhaustion Death may occur (43–45, 48, 49, 52)	Severe complications, i.e., rhabdomyolysis with elevated creatine phosphokinase, myoglobinuria, renal failure and intravascular thrombosis with pulmonary embolism and respiratory failure (4, 5, 8, 14, 16) Possible 20%–30% mortality rate with full syndrome (7, 12, 16, 19, 20)
Treatment	Neuroleptic and other treatments to reduce severe psychotic symptoms	Immediate cessation of all dopamine-blocking neuroleptics Dopamine agonists (to reduce central hypodopaminergic state), calcium channel blockers (to reduce muscle rigidity), β -adrenergic blockers (to reduce tachycardia), other supportive measures as needed

hausted that he could be kept in bed for several hours. Toward evening, he developed a parotitis and fever, which reached 40 °C the next morning but fell after surgical drainage. The psychomotor excitement continued: He attempted to throw himself out of bed and to bite anyone who came near. Heavy doses of chloral hydrate induced only a few hours of sleep. He refused all food. His body was covered with hematomas. Within a few hours he died. His blood count showed no anemia and no changes reflecting inflammation.

Case 2: neuroleptic malignant syndrome (from reference 5). A 22-year-old man, who had received past treatment with haloperidol, was admitted to the hospital for agitation and violent outbursts. He received haloperidol, 5 mg every 2 hours, and benztropine mesylate, 2 mg i.m. twice a day. Three days later he remained agitated and confused. Haloperidol was stopped, and thiothixene, 5 mg every 4 hours, was begun. He continued receiving the same dose of benztropine mesylate. Approximately 24–36 hours later, the patient was verbally unresponsive, catatonic, sweating, and dehydrated and had a fever (38.3–39.4 °C) and tremors. He was treated with intravenous fluids and continued intramuscular benztropine mesylate. His serum creatine phosphoki-

nase level was 498 U/liter. He was transferred to another hospital, where he was noted to have extreme rigidity, fluctuating consciousness, profuse diaphoresis, generalized tremors, tachycardia (110–136 beats/minute), and tachypnea (up to 40 respirations/minute). His blood pressure varied between 120 and 160 mm Hg systolic and between 80 and 100 mm Hg diastolic. His temperature at admission was 37.2 °C and increased to 39.4 °C; he was without documented infection. He had difficulty swallowing and required tracheal intubation. His WBC count and differential were normal at admission, but his WBC count became elevated to 18,100/mm³. The results of a head CT scan, EEG, and lumbar puncture were normal.

His symptoms were diminished by 70 mg of intravenous dantrolene, but less than 1 hour after the infusion was completed, he again had total body rigidity and diaphoresis. He was treated with intravenous hydration, dantrolene, 50 mg every 6 hours by nasogastric tube, and bromocriptine, 5–7 mg every 8 hours by nasogastric tube, and improved significantly. Up to 160 mg/day of propranolol was given to control tachycardia. Both dantrolene and bromocriptine were discontinued after 48 hours, when results of liver function tests suggested a drug-induced hepatitis. Along with this treatment, he had received intravenous amobarbital sodium,

i-100 mg/hour for 5 days, after a trial dose had produced marked decrease in rigidity. The patient's neuroleptic malignant syndrome resolved with supportive care. His serum creatine phosphokinase level reached a maximum of 8882.5 /liter and became normal in about 1 month.

DISCUSSION

Some aspects of the clinical contrast between the two syndromes bear comment. Investigators have argued that muscle rigidity is present in both syndromes (22, 23, 25, 27). However, for patients with neuroleptic malignant syndrome, the severity and progressive, relentless nature of the muscle hypertonicity and its quality of "lead pipe" rigidity are so characteristic and prominent that muscle rigidity is generally considered an essential feature for the diagnosis (5, 7, 10, 15, 16, 44). On the other hand, muscle rigidity may or may not be present in lethal catatonia (38, 43, 44, 48) and present is intermittent and alternates with a full range of motion; i.e., it has catatonic-like features (40, 5, 52). In the final stages of exhaustion, the degree of rigidity may depend on the patient's remaining muscular strength.

The findings of this review challenge the notion that lethal catatonia is clinically indistinguishable from neuroleptic malignant syndrome. The lethality of lethal catatonia appears to be a result of the severe cachexia, weakness, fever, and dehydration secondary to the increased motor and mental activity of the catatonic psychosis (40, 41, 43, 44, 48-50, 52). In contrast, neuroleptic malignant syndrome does not appear clinically as a form of severe excitement but rather as a severe drug reaction characterized by muscle rigidity, autonomic instability, alteration of consciousness, and fever (5, 7-10, 13-17). Furthermore, even if exhaustion is a sequela of the sustained muscle rigidity in neuroleptic malignant syndrome, death usually results from other causes, such as severe hyperpyrexia, pulmonary embolus, acute renal failure secondary to rhabdomyolysis, acute respiratory failure secondary to respiratory muscle paralysis, hepatic failure, and myocardial infarction (4, 5, 8, 14, 16).

With regard to the treatment of neuroleptic malignant syndrome, the first consideration is that all neuroleptics should be stopped (5, 7-14, 16). Because the pathogenic mechanism of neuroleptic malignant syndrome is thought to be severe CNS postsynaptic dopamine receptor blockade (6, 13, 14, 16), centrally acting dopamine agonists, such as bromocriptine, L-dopa, and amantidine, may be indicated (9, 10, 11, 13, 16). However, these agents can produce or worsen manic or excited behavior, as well as psychotic symptoms, and could be detrimental in catatonic excitement. Because the catatonic exhaustion syndrome is a psychotic illness, treatment can include dopamine-blocking neuroleptics as well as ECT (22, 28-30, 53). The present review is by no means exhaustive, and other approaches to comparing these syndromes are

also useful. For example, Mann et al. (22), on the basis of a literature survey of 292 cases of lethal catatonia, suggested that neuroleptic malignant syndrome is a severe, iatrogenic (drug-induced) type of lethal catatonia, and Kellam (54) questioned whether catatonic schizophrenia, other catatonias, and neuroleptic malignant syndrome represent the same syndrome. We prefer to emphasize the contrasts between the two syndromes. Further elucidation of the differences in these syndromes as well as their similarities should aid clinicians in their prevention, early detection, and treatment.

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Sleep EEG and DST Findings in Anergic Bipolar Depression

Michael E. Thase, M.D., Jonathan M. Himmelhoch, M.D., Alan G. Mallinger, M.D.,
David B. Jarrett, M.D., Ph.D., and David J. Kupfer, M.D.

The authors report sleep EEG and dexamethasone suppression test (DST) findings for a homogeneous sample of anergic bipolar depressed outpatients (bipolar I, N=7; bipolar II, N=19) characterized by motor retardation, volitional inhibition, hypersomnia, or weight gain and sleep EEG findings for 26 age- and sex-matched normal control subjects. Sleep architecture was abnormal in bipolar depression, particularly with respect to little stage 1 sleep. The biological profile of an anergic episode of bipolar depression did not include a shorter than normal mean REM latency, poor sleep continuity, or abnormally low amounts of stages 3 and 4 sleep, and only three (13%) of 23 patients manifested cortisol nonsuppression.

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The depressed phase of bipolar affective disorder may assume many clinical forms, ranging from mild states of apathy and anergia to severe agitated or delusional melancholia. Studies of biological processes in bipolar depression also reveal considerable variability, particularly when all-night EEG sleep studies or hypothalamic-pituitary-adrenocortical (HPA) axis activity is examined. For example, several groups have documented the occurrence of hypersomnia in bipolar depression (1, 2), and other investigators have found the more typical disturbances of sleep continuity or low amounts of slow wave sleep in bipolar and unipolar depression (3, 4). Similarly, REM latency has been reported to be either short (1-3) or normal (4-6) in bipolar depression. With respect to the dexamethasone suppression test (DST), nonsuppression rates have been

reported to be high (7), low (8), or equivalent (9-11) in comparisons of bipolar and unipolar depression.

The current study was conducted to help clarify the frequency of disturbances in these psychobiological indicators by focusing on a homogeneous clinical sample of bipolar depressed patients. Our sample consisted of outpatients in a current episode of nonpsychotic bipolar depression who manifested clinical features of motor retardation, anergia, hypersomnia, or weight gain. We have previously referred to this clinical profile as anergic depression (12), and there is some evidence that it is overrepresented in the depressed phase of bipolar illness (13-18). Moreover, we have focused on anergic symptoms as part of ongoing research on the treatment of bipolar depression. Preliminary clinical evidence collected by our group suggests that the anergic phase of bipolar depression may respond preferentially to treatment with more stimulating antidepressants, such as the monoamine oxidase inhibitor (MAOI) tranylcypromine (12, 19).

METHOD

Our subjects included 26 patients with bipolar affective disorder and 26 normal age- and sex-matched control subjects. The control subjects were recruited from newspaper advertisements or were relatives of staff members. They were unmedicated, and the absence of any psychiatric history was confirmed on the basis of an evaluation with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (20). Prospective patients initially were diagnosed as meeting the criteria for bipolar affective disorder, depressed phase, according to *DSM-III*. Initial diagnoses were based on interviews conducted by nurse clinician/faculty psychiatrist teams utilizing our institute's standardized, semistructured initial evaluation (21). The diagnosis of primary bipolar depression subsequently was independently confirmed by Research Diagnostic Criteria (22) diagnoses, which were based on a semistructured interview conducted by an experienced clinical psychologist and supervised by one of us (M.E.T., J.M.H.). Prospective patients with concurrent diagnoses of alcoholism or drug abuse, borderline or antisocial personality disorder, mental retardation, schizophrenia, schizoaffective disorder, seizure disorder, or psychotic episode of major depression were excluded.

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Patients with rapid cycling forms of bipolar disorder (i.e., four or more episodes each year) and patients with a history of nonresponse or intolerance to the antidepressants tranylcypromine and imipramine (i.e., the medications used in our protocols) also were excluded.

All prospective subjects were given a comprehensive physical evaluation, during which laboratory studies, including CBC, blood chemistry, thyroid function, thyroid-stimulating hormone level, liver function, syphilis serology, urinalysis, chest X-ray, ECG, and routine waking EEG, were performed. Any subject with evidence of intercurrent medical conditions associated with depression or contraindicating the use of antidepressant medications was excluded.

In addition, all patients scored 15 or higher on the first 17 items of the Hamilton Rating Scale for Depression (23) at screening and after a supervised 14-day drug- and alcohol-free evaluation. Their mean \pm SD level of severity on the Hamilton scale after the evaluation period was 21.5 ± 3.2 , which indicated a moderate to severe level of depression for an outpatient sample. The patients also met our operational definition of anergic depression: the presence in the current episode of 1) definite anergia (score of 2 on Hamilton scale item 13) and psychomotor retardation (score of 2 or more on item 8) and 2) at least one of two associated reversed neurovegetative features (weight gain, i.e., 2.2 kg or more, and hypersomnia, i.e., 1 hour or more of extra sleep a day than "usual"). Although we consider these criteria for an anergic episode of depression to be tentative, these criteria identified 26 (79%) of 33 consecutive bipolar outpatients referred to our research clinic. We did not include the remaining seven nonanergic patients in this protocol. All patients and control subjects provided written informed consent for protocol participation, which for the patients also included completing a DST.

The mean \pm SD age of the 26 patients (nine men and 17 women) was 37.2 ± 10.1 years, and the mean \pm SD length of their current episode of depression was 4.3 ± 6.0 months. The mean \pm SD age of onset of their bipolar illness was 23.8 ± 7.9 years, the mean \pm SD number of prior depressive episodes was 7.3 ± 3.5 , and the mean \pm SD number of prior hypomanic/manic episodes was 7.2 ± 4.1 . Seven patients met the criteria of Fieve and Dunner (24) for bipolar I disorder on the basis of at least one past episode of mania that required inpatient treatment; the remaining 19 patients were classified bipolar II on the basis of milder past episodes of mania or hypomania.

During the 2-week drug- and alcohol-free washout, the patients were seen weekly and were asked to keep a diary recording their sleep-wake cycle and any use of medication or alcohol. After review of these materials to confirm the validity of the washout, EEG sleep studies were completed over 2 consecutive nights in our outpatient sleep evaluation center. Our methods for conducting and scoring EEG sleep studies have been published elsewhere (25). All subjects normally retired to their rooms and the lights were turned off by 11:30 p.m. at the latest; they were allowed to sleep until 7:00

a.m. the next morning. All sleep records were scored by certified polysomnographic technologists without knowledge of clinical diagnosis.

To lessen the number of statistical comparisons between the bipolar depressed and normal control samples the 22 sleep EEG variables of interest were conceptually grouped into three categories: sleep continuity variables (time spent asleep, sleep latency, time spent awake, number of awakenings, and sleep efficiency), sleep architecture variables (minutes and percent of stages 1, 2, 3, and 4 and REM sleep), and REM sleep variables (number of REM periods, the latency, density, and activity of REM sleep, and the length, activity, and density of the first REM period). To further control for the possible confounding influences of age and first-night adaptation effects, data from each category were analyzed with a multivariate analysis of covariance (MANCOVA) with repeated measures (night 1 versus night 2). These analyses yielded effects for age (the covariate), diagnosis (anergic bipolar depressed patients versus control subjects), and night (night 1 versus night 2), as well as the possible interaction between diagnosis and night. Univariate ANCOVAs were performed after the MANCOVAs if significant main effects or interactions were found.

In addition to performing the multivariate analyses, we wanted to determine whether the groups differed with respect to a categorical definition of REM latency. Consistent with our prior work, a 2-night mean REM latency value of 60 minutes or less was considered abnormally short. Significance of the resultant 2×2 contingency table was tested with the chi-square statistic with Yates' correction.

A 1.0-mg DST (26) was completed for 23 of the 26 patients on the day after completion of the EEG sleep studies. A blood sample was drawn at 4:00 p.m. on the first day for determination of a baseline plasma cortisol level; patients took 1.0 mg of dexamethasone at home at 11:00 p.m. that evening, and a 4:00 p.m. blood sample was obtained the next day for determination of postdexamethasone plasma cortisol. All plasma cortisol concentrations were measured by radioimmunoassay. A postdexamethasone plasma cortisol value of 4 μ g/dl or less was used as the criterion for nonsuppression; this value was based on procedures established in the psychoneuroendocrinology laboratory of one of us (D.B.J.). The DST was not completed for the control subjects.

RESULTS

The patients and control subjects did not differ significantly on the variables assessing sleep continuity (table 1); overall sleep efficiency was virtually identical in both groups. The groups differed on the measures of sleep architecture (table 2), principally due to fewer minutes (and lower percent) of stage 1 sleep in the bipolar patients than in the control subjects ($F=18.2$,

TABLE 1. EEG Sleep Characteristics of Anergic Bipolar Depressed Outpatients and Age- and Sex-Matched Control Subjects

EEG Sleep Variable	Two-Night Values			
	Bipolar (N=26)		Control (N=26)	
	Mean	SD	Mean	SD
sleep continuity indexes				
Time spent asleep (min)	389.8	54.1	380.8	34.9
Sleep latency (min)	17.6	10.1	19.5	14.5
Time spent awake (min)	27.8	36.8	21.6	23.3
Number of awakenings (min)	4.8	2.3	5.4	3.8
Sleep efficiency (%)	89.6	7.8	90.4	6.9
sleep architecture indexes				
Stage 1				
Minutes	19.4	13.9	35.9	17.4
Percent	4.9	3.3	9.6	5.2
Stage 2				
Minutes	249.4	41.8	231.0	44.2
Percent	64.0	7.7	60.5	9.5
Stage 3				
Minutes	21.9	16.7	25.0	22.2
Percent	5.7	4.8	6.5	5.9
Stage 4				
Minutes	10.3	18.7	9.8	17.0
Percent	2.7	5.0	2.5	4.3
REM				
Minutes	88.6	24.8	78.7	19.3
Percent	22.6	5.3	20.7	4.8
REM indexes				
Number of REM periods	3.7	0.9	3.8	0.7
REM activity (units)	112.4	57.3	90.2	36.9
REM density (units/min)	1.2	0.4	1.2	0.5
REM latency (min)	71.8	33.0	72.8	24.1
First period				
REM activity (units)	20.4	18.8	12.6	10.4
REM density (units/min)	1.0	0.4	0.8	0.5
REM time (min)	18.8	13.0	14.4	8.1

$t=1$, 49, $p<0.001$, and $F=20.5$, $df=1$, 49, $p<0.001$, respectively). There also was a trend for more REM time in the bipolar group ($F=3.2$, $df=1$, 49, $p=0.07$). The other REM sleep values, including mean REM latency and REM density, did not significantly differentiate the groups (tables 1 and 2); however, a significantly greater proportion of the bipolar depressed patients (13 of 26) than the control subjects (six of 26) had 2-night mean REM latency values of 60 minutes or less ($\chi^2=4.34$, $df=1$, $p<0.05$, two-tailed, with Yates' correction).

Consistent with findings from prior studies (25), the effects for age (the covariate) on sleep continuity and sleep architecture were significant (table 2). Univariate analyses documented a lighter, more fragmented sleep in older subjects on most measures of sleep continuity and sleep architecture. Age was not significantly related to the REM sleep variables. Significant first-night adaptational effects were found on measures of sleep continuity and REM sleep but not on sleep architecture (table 2). As previously described (25), sleep continuity and generation of REM sleep improved on the second night of study. However, there were no significant interactions between diagnostic group and night of EEG sleep recording, indicating that the adaptation-

al process was similar in anergic bipolar depressed patients and healthy control subjects.

The mean \pm SD baseline plasma cortisol level for the anergic bipolar depressed patients was 8.6 ± 4.7 $\mu\text{g/dl}$ (range, 5.5–21.9 $\mu\text{g/dl}$), and their mean \pm SD postdexamethasone level was 1.5 ± 3.6 $\mu\text{g/dl}$ (range, 0.3–8.8 $\mu\text{g/dl}$). Only five (22%) of the 23 patients had baseline plasma cortisol concentrations greater than 15 $\mu\text{g/dl}$, and only three (13%) manifested cortisol nonsuppression on the DST. Consistent with findings from several other studies (27–30), all six patients with either high baseline cortisol values or postdexamethasone nonsuppression also had REM latency values of 60 minutes or less.

DISCUSSION

A majority of our 26 anergic bipolar depressed outpatients did not manifest the more characteristic EEG sleep and cortisol disturbances of depression (e.g., impaired sleep continuity, low amounts of stages 3 and 4 sleep, hypercortisolemia, and postdexamethasone nonsuppression). The bipolar patients also did not differ from matched control subjects with respect to sleep continuity disturbances and mean REM latency. Furthermore, unlike findings from other studies of depressed patients (31), our anergic bipolar depressed patients showed the same type of adaptational changes in the sleep laboratory as the normal control subjects. The EEG sleep profiles of the bipolar depressed sample could not be considered normal, however, as alterations of sleep architecture were observed and a significantly greater proportion of patients than control subjects had categorically shortened REM latency.

The hypersomnic characteristics of a majority of our patients may account for the rather atypical sleep profiles (relative to prior studies of depression), particularly with respect to the lower than normal amount of light stage 1 sleep and the trend for higher than normal generation of REM sleep. Longer than normal REM sleep time has been reported previously in "natural long sleepers" (32) and in a presumably unipolar group of young depressed patients with hypersomnia (33). Our EEG sleep protocol may have been less sensitive for detection of hypersomnia than the method used by Hawkins et al. (33), because our subjects were not permitted to sleep past 7:00 a.m.

Our findings may help clarify inconsistencies apparent in prior studies of EEG sleep and the DST in bipolar depression. Several early reports from our group (1, 31) noted shortened REM latency and hypersomnia in bipolar depressed inpatients and a relative absence of sleep continuity disturbances compared to unipolar depressed patients. The results of subsequent investigations at the University of Michigan (2, 34) have tended to support these observations. Nevertheless, observed EEG sleep differences between unipolar and bipolar depressed patients may be explained by differences in age, severity of depression, or inpatient/outpatient sta-

TABLE 2. Summary of MANCOVA for Sleep Variables in 26 Anergic Bipolar Depressed Outpatients and 26 Age- and Sex-Matched Control Subjects

Sleep Variable	Effect for Age Covariate		Main Effect				Night by Group Interaction	
	F	df	Night		Group		F	df
			F	df	F	df		
Sleep continuity	3.3 ^a	5, 45	2.9 ^a	5, 46	0.9	5, 45	0.9	5, 46
Sleep architecture	2.3 ^a	10, 40	0.8	10, 41	3.1 ^b	10, 40	1.0	10, 40
REM sleep	1.3	7, 43	2.9 ^a	7, 43	1.3	7, 43	1.1	7, 44

^ap<0.02.^bp<0.001.

tus. Consistent with this notion, Duncan et al. (3) found fewer EEG sleep differences between unipolar and bipolar depression in a more severely ill inpatient sample. Across several recent studies (2, 3, 5, 6), however, bipolar depression appears to differ from unipolar disorder with respect to the generation of a normal amount of slow wave (stages 3 and 4) sleep; a recent report by Hudson et al. (35) suggests that slow wave sleep also is normal during the manic phase of bipolar illness. It remains to be seen if preservation of slow wave sleep in bipolar disorder represents an epiphenomenon of age or severity differences or, conversely, truly distinguishes between unipolar and bipolar affective disorders.

The 13% cortisol nonsuppression rate on the DST that we detected in our 26 patients is substantially lower than the rates published in several investigations of bipolar disorder (7, 9) and approaches the rates observed in normal control samples (26). Schatzberg et al. (8) also found a significantly lower rate of nonsuppression on the DST in bipolar than in unipolar depressed patients and high nonsuppression rates that were linked to the presence of psychotic features in unipolar patients. Our inability to collect an 11:00 p.m. postdexamethasone plasma sample probably lowered our observed rate somewhat (26), although Schlessner et al. (7), using only a single 8:00 a.m. sample, found an 85% (28 of 33) nonsuppression rate in hospitalized patients with bipolar depression. Extrapolation of these findings suggests that the clinical profile of the depressive syndrome influences DST results, i.e., that depressions characterized by reversed neurovegetative symptoms are not linked to HPA axis hyperactivity. Also, preliminary results of ongoing studies of atypical nonbipolar depression indicate similar EEG sleep (36) and cortisol profiles (37) to those seen in the current study, and James et al. (38) found low cortisol nonsuppression rates on the DST in patients with seasonal affective disorder. Our patients share a number of clinical similarities with the seasonal affective disorder profile. To ascertain the overlap between our definition of anergic bipolar depression and seasonal affective disorder, we reviewed case histories of patients' index and past episodes of depression and found that only six (23%) of 26 had the regular periodicity of fall-winter depressions necessary for this diagnosis.

Thus, only a minority of our patients could be described as also having seasonal affective disorder.

Our results also raise interesting questions about the pathophysiology and treatment of anergic bipolar depression. We have identified a subgroup of bipolar depressed patients with a presumably endogenous, cyclical mood disorder who 1) do not manifest prominent signs of activation of the HPA axis, 2) generate little light stage 1 sleep and a normal amount of slow wave sleep, and 3) have little disturbance of sleep efficiency. On the other hand, there was a trend for REM sleep time to be longer than normal in these patients, quite unlike the diminution in REM sleep we have described in unipolar and bipolar psychotic depressions (39). We suggest that treatment of anergic bipolar depression with sedating agents such as tertiary tricyclics may not prove to be the optimal match of pharmacological action with symptom profile and, perhaps, underlying neurobiological disturbance. Conversely, MAOIs such as tranylcypromine are not sedating yet (like the tricyclics) are potent REM suppressors (40). The utility of such a speculation, of course, rests on demonstration of the antidepressant superiority of an MAOI to a standard tricyclic in anergic bipolar depression.

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Briquet's Syndrome in Association With Depression and Panic: A Reconceptualization of Briquet's Syndrome

Herbert Orenstein, M.A., M.D.

In a sample of 188 consecutive female psychiatric patients, Briquet's syndrome was found to be associated more closely with the aggregation of both major depression and either panic disorder or agoraphobia than with major depression or panic disorder-agoraphobia alone. These results are consistent with the hypothesis of a shared diathesis underlying some cases of major depression, panic disorder, agoraphobia, and Briquet's syndrome. The author proposes that Briquet's syndrome may represent the most extreme expression of a tendency for a number of physical and psychological syndromes to aggregate.

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Although classified by *DSM-III* as a somatoform disorder, somatization disorder (Briquet's syndrome) is known to share a number of clinical features in common with affective and anxiety disorders. This is reflected in the fact that symptoms such as panic attacks, nervousness, depressed feelings, and suicide attempts are used to diagnose Briquet's syndrome by Feighner criteria (1). Clinical studies of patients with Briquet's syndrome have shown that they often present for treatment complaining of depression (2) or panic attacks (3).

Patients with both major depression and panic attacks have been described as hypochondriacal, sexually dysfunctional, chronically depressed, and poorly responsive to treatment (4-6). These features are typical of Briquet's syndrome and raise the possibility that Briquet's syndrome may be associated with the aggregation of major depression and panic attacks. Supporting such an association, an epidemiologic survey looking at the strength with which psychiatric disorders are paired in a community population (7) found that in-

dividuals with somatization disorder had 96.5 times the odds of having panic disorder, 27.3 times the odds of having agoraphobia, and 24.6 times the odds of having major depression as did persons without somatization disorder.

Previous studies have pointed to a high rate of major depression among patients with panic disorder or agoraphobia (panic-agoraphobia) (8) and have suggested that there may be a partially shared diathesis between panic disorder and major depression (9). My hypothesis, which argues that the linkage between major depression and panic-agoraphobia may be associated, in turn, with Briquet's syndrome, suggests that a shared diathesis may underlie some cases of panic disorder, agoraphobia, major depression, and Briquet's syndrome. This would account for a number of parallels in the family histories of patients with these disorders, including the elevated rate of alcoholism reported in relatives of patients with panic disorder (10), agoraphobia (11), major depression (12), or Briquet's syndrome (3) and the elevated rate of antisocial personality disorder reported in relatives of patients with major depressive disorder (12, 13) or Briquet's syndrome (3).

To test the hypothesis that Briquet's syndrome may be associated with the aggregation of both major depression and either panic disorder or agoraphobia, structured interviews were administered to 188 consecutive female psychiatric patients. As expected, Briquet's syndrome was found to be more frequent in patients with a lifetime history of both major depression and either panic disorder or agoraphobia with panic attacks (depression-panic-agoraphobia) than in patients with a lifetime history of major depression or panic-agoraphobia alone.

METHOD

I administered a structured interview that included the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (14) to 188 consecutive female psychiatric patients. The interview also included specific questions about past and present medical symptoms, procedures, and diagnoses. Patients were excluded from the study if they had any history of psychosis, were currently suffering from an organic mental disorder, or were seen in connection

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with legal or disability evaluations. All patients but one were white. They ranged in age from 14 to 78 years (mean \pm SD=38.2 \pm 13.3 years). All patients gave informed consent to participate in the study.

The original purpose of the study was to explore the relationship between certain somatic and psychological complaints in psychiatric patients (15). The hypothesis of an association between Briquet's syndrome and depression-panic-agoraphobia was not formulated until after completion of the data-gathering phase of the study.

To assess interrater diagnostic reliability, a senior psychiatrist and I administered the SADS-L to 20 patients on a blind basis. Our overall diagnostic agreement was 90% (15).

Briquet's syndrome was diagnosed according to Feighner criteria (1) rather than *DSM-III* because Feighner criteria have been more extensively researched (16) and allow the diagnosis of "probable" Briquet's syndrome, which is helpful in identifying less extreme polysymptomatology. According to Feighner criteria, a diagnosis of definite Briquet's syndrome requires the presence of at least 25 symptoms, and diagnosis of probable Briquet's syndrome requires the presence of at least 20 symptoms in nine of 10 symptom categories. Other psychiatric diagnoses were made on a lifetime basis according to *DSM-III* criteria. More than one diagnosis per patient was allowed.

Because of previous suggestions that panic attacks may play a central role in the development of agoraphobia (17) and because all patients with agoraphobia in the present study had a history of panic attacks, patients with either panic disorder or agoraphobia with panic attacks were pooled. In accord with *DSM-III*, panic disorder and agoraphobia with panic attacks were diagnosed only if they occurred independently of episodes of major depression. Patients were designated as having a lifetime history of depression-panic-agoraphobia even if their episodes of major depression and panic-agoraphobia had not overlapped.

Characteristic health complaints typically seen in Briquet's syndrome include sickliness, multiple surgeries, and conversion, psychosexual, and menstrual symptoms (3, 18). To help validate the diagnosis of Briquet's syndrome, specific statistical comparisons were made between patients with Briquet's syndrome and other patients regarding these complaints. In this and other analyses, health complaints were divided for scoring purposes into previously described symptom categories (19). The psychological categories were depression, psychosexual, and anxiety. The somatic categories were menstrual, irritable bowel, somatic anxiety, gastrointestinal, conversion, and pain. Because of previous reports of elevated rates of Briquet's syndrome in patients with ovarian cysts (19) or irritable bowel syndrome (20), the frequency of these disorders in patients with Briquet's syndrome was compared with that in patients with other disorders.

Statistical comparisons for categorical variables were made by using Yates'-corrected chi-square or

Fisher's exact tests. The effect of major depression and panic disorder on the frequency of health complaints was assessed by a two-way analysis of variance (ANOVA). Other continuous variables were compared by using *t* tests. All probability levels were two-tailed.

RESULTS

Lifetime *DSM-III* diagnoses of the 188 patients were as follows: 110 had major depression, 53 had agoraphobia with panic attacks, 35 had other phobic disorders, 25 had panic disorder, 21 had dysthymic disorder, 21 had substance use disorders, 20 had somatoform disorders, 12 had other affective disorders, nine had adjustment disorders, and 21 had other disorders. More than one diagnosis per patient was permitted. According to Feighner criteria, 16 (9%) of the 188 patients had definite Briquet's syndrome and 27 (14%) had definite or probable Briquet's syndrome. None of the patient groups described in this paper differed significantly from any other in age.

As predicted, a significant relationship was found between Briquet's syndrome and a lifetime history of depression-panic-agoraphobia. Ten (19%) of the 52 patients with a lifetime history of depression-panic-agoraphobia were found to have definite Briquet's syndrome, compared with six (4%) of 136 other patients ($\chi^2=8.79$, *df*=1, *p*<0.003). The 19% frequency of definite Briquet's syndrome found among these 52 patients with depression-panic-agoraphobia was significantly higher than that found among the 58 patients with major depression alone, three (5%) of whom had definite Briquet's syndrome (*p*<0.04, Fisher's exact test), but it was not significantly higher than that found among the 26 patients with panic-agoraphobia alone, one (4%) of whom had definite Briquet's syndrome (*p*<0.09, *n.s.*, Fisher's exact test). When the definition of Briquet's syndrome was broadened to include probable cases, the results became more uniformly significant. Sixteen (31%) of the 52 patients with depression-panic-agoraphobia were found to have definite or probable Briquet's syndrome, compared with seven (12%) of the 58 patients with depression alone ($\chi^2=4.72$, *df*=1, *p*<0.03) and two (8%) of the 26 patients with panic-agoraphobia alone ($\chi^2=3.98$, *df*=1, *p*<0.05).

To help validate the diagnosis of Briquet's syndrome, the health histories of the 27 patients with definite or probable Briquet's syndrome were compared with those of the remaining 161 patients. As shown in table 1, patients with Briquet's syndrome reported significantly more complaints than other patients in the conversion, psychosexual, and menstrual symptom categories. As shown in table 2, patients with Briquet's syndrome were significantly more likely than other patients to report sickliness, a previous medical diagnosis of irritable bowel syndrome or ovarian cysts, and a history of three or more major surgeries.

Results of the two-way ANOVA are shown in table

TABLE 1. Conversion, Psychosexual, and Menstrual Symptom Category Scores of 188 Consecutive Female Psychiatric Patients With or Without Definite or Probable Briquet's Syndrome*

Symptom Category	Score				t (df=186)	p
	Briquer's Syndrome (N=27)		All Other Patients (N=161)			
	Mean	SD	Mean	SD		
Conversion	2.04	1.48	0.35	0.69	5.80	0.0000
Psychosexual	1.63	0.97	0.77	0.85	4.75	0.0000
Menstrual	1.81	1.04	1.02	0.86	3.74	0.0007

*Details of symptom category scoring are given elsewhere (19).

TABLE 2. Health Histories of 188 Consecutive Female Psychiatric Patients With or Without Definite or Probable Briquet's Syndrome

Health History Item	Briquet's Syndrome (N=27)		All Other Patients (N=161)		χ^2 (df=1)	p
	N	%	N	%		
Sickliness	18	67	15	9	48.66	0.000
Three or more major surgeries	14	52	22	14	19.38	0.000
Medical diagnosis of ovarian cysts	10	37	26	16	5.24	0.022
Medical diagnosis of irritable bowel syndrome	13	48	32	20	8.66	0.003

3. Major depression and panic-agoraphobia both were found to have significant effects on the frequency of health complaints in all symptom categories except those pertaining to menstrual and irritable bowel complaints. Interactions between major depression and panic-agoraphobia were not statistically significant except in the psychosexual and menstrual symptom categories.

DISCUSSION

Patients with panic disorder or agoraphobia have been found to have a high rate of major depression (8). It was precisely this subgroup of patients with a lifetime history of panic disorder or agoraphobia and a tendency toward episodes of major depression who showed a particularly high rate of Briquet's syndrome in the present study. These results raise questions about the categorical distinctions made by *DSM-III* between somatization disorder on the one hand and major depression, panic disorder, and agoraphobia on the other and suggest that somatization disorder may be closely related to some anxiety and affective disorders. The present findings are consistent with the possibility of a shared diathesis underlying some cases of major depression, panic disorder, agoraphobia with panic attacks, and Briquet's syndrome. These results also fit the model of psychopathology proposed by Foulds and Bedford (21), which predicts a high degree

of diagnostic overlap between neurotic disorders, such as Briquet's syndrome, and dysthymic states, such as anxiety or depression.

Previous studies have noted somatizing tendencies in patients with panic disorder (22) or depression (23) and have reported that depression and anxiety are the two major psychiatric syndromes seen by primary care physicians (23). A study of patients with panic disorder or agoraphobia found a trend toward an association between somatic symptoms and a history of major depressive episodes (24). The present results are consistent with these reports and suggest that Briquet's syndrome may be associated more closely with the aggregation of major depression and panic-agoraphobia than with occurrences of either disorder alone. The paucity of significant interactions in the present ANOVA suggests that the symptom-generating effect of major depression and panic-agoraphobia may be additive rather than multiplicative.

The present finding of definite Briquet's syndrome in 16 (9%) of 188 consecutive female psychiatric patients is comparable to the 6%–10% rate of Briquet's syndrome reported in previous studies (2, 25). In the present study, 13 (81%) of 16 patients with definite Briquet's syndrome reported a lifetime history of major depression and 11 (69%) reported a lifetime history of spontaneous panic attacks, including two patients with infrequent attacks and nine others with panic disorder or agoraphobia. These figures are comparable to the 87% lifetime rate of major depression (16) and the 74% rate of panic attacks (26) found in previous studies of patients with Briquet's syndrome. Although previous studies have reported higher than expected rates of Briquet's syndrome among patients with ovarian cysts (19) or irritable bowel syndrome (20), this is the first study, to my knowledge, to demonstrate a higher rate of irritable bowel syndrome or ovarian cysts in patients with Briquet's syndrome.

The diagnosis of Briquet's syndrome is often overlooked, especially in patients with prominent psychological symptoms (27). In part, this may reflect the fact that depressive symptoms in Briquet's syndrome are identical to those seen in primary depression in the course of other psychiatric illnesses (28). One implication of the present study is that a high index of suspicion for Briquet's syndrome is advisable whenever evaluating women with a history of both panic attacks and depression.

The tendency for Briquet's syndrome to be overlooked as a diagnosis, coupled with the high rate of major depression and panic attacks in women with Briquet's syndrome, raises the possibility that women with Briquet's syndrome sometimes may be included in clinical research studies of major depression or panic-agoraphobia without being identified as having Briquet's syndrome. This possibility may help to explain a number of observations in the psychiatric literature. For example, patients with both major depression and panic attacks have been reported to show hypochondriasis (4, 5), chronicity (5), poor response to treat-

TABLE 3. Effect of Major Depression and Panic Disorder or Agoraphobia on the Frequency of Health Complaints in 188 Consecutive Female Psychiatric Patients

Symptom Category ^a	Score								Two-Way ANOVA			
	Depression and Panic-Agoraphobia (N=52)		Depression Only (N=58)		Panic-Agoraphobia Only (N=26)		Neither (N=52)		Depression Factor		Panic-Agoraphobia Factor	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df=1, 184)	p	F (df=1, 184)	p
Psychological total	8.50	1.54	5.86	1.97	4.42	2.12	2.71	1.79	165.45	0.0000	59.92	0.0000
Depression	4.39	0.97	3.86	1.48	1.62	1.65	1.15	1.24	183.13	0.0000	5.91	0.0160
Psychosexual ^b	1.40	0.93	0.85	0.85	0.58	0.90	0.60	0.77	16.50	0.0001	4.16	0.0429
Anxiety	2.71	0.54	1.16	0.88	2.23	0.71	0.96	0.84	8.32	0.0044	146.06	0.0000
Somatic total	11.87	4.88	7.17	3.48	8.12	4.59	5.10	2.92	23.16	0.0000	40.59	0.0000
Menstrual ^c	1.44	1.00	1.02	0.96	0.89	0.99	1.10	0.69	2.93	0.0887	0.58	0.4464
Irritable bowel	1.67	0.92	1.17	0.99	1.39	0.85	1.02	0.98	2.28	0.1324	8.78	0.0034
Somatic anxiety	2.67	1.42	1.76	0.92	2.19	1.47	1.06	1.06	10.38	0.0015	31.20	0.0000
Gastrointestinal	2.08	1.56	1.09	0.96	1.39	0.98	0.69	0.85	9.71	0.0021	23.31	0.0000
Conversion	1.27	1.25	0.35	0.69	0.65	1.36	0.17	0.43	7.44	0.0070	23.72	0.0000
Pain	2.27	1.39	1.71	1.11	1.54	1.42	1.02	0.90	15.14	0.0001	8.80	0.0034
Overall total	20.37	5.69	13.03	4.14	12.58	5.75	7.79	4.14	76.76	0.0000	66.36	0.0000

^aA higher score indicates more symptoms; details of symptom category scoring are given elsewhere (19).

^bSignificant interaction effect of depression and panic-agoraphobia ($F=4.77$, $df=1$, 184, $p=0.0302$).

^cSignificant interaction effect of depression and panic-agoraphobia ($F=5.18$, $df=1$, 184, $p=0.0240$).

ment (6, 29), and lifelong problems with sexual dysfunction (4), all of which are typical features of Briquet's syndrome. The association of Briquet's syndrome with depression-panic-agoraphobia may play a role in other findings, such as chronicity and poor social adjustment among patients with both anxiety neurosis and secondary depression (30), poor response to antidepressant medication in patients with anxious depression (31), and poor prognosis in depressed patients with anxiety symptoms and anxious patients with depression (32). An excess of Briquet's syndrome among patients with both agoraphobia and a lifetime history of major depression may explain, in part, the high rate of sexual dysfunction (33), gynecological surgery (34), hypochondriacal concerns (33), and chronicity (35) reported in agoraphobia.

The present findings suggest the hypothesis that Briquet's syndrome may represent the most extreme expression of an underlying tendency present in the general population for a number of physical and psychological syndromes to aggregate. These syndromes, which may include major depression with onset before age 40, panic disorder, agoraphobia, antisocial personality disorder, and alcoholism, appear to aggregate along sexual lines—major depression, panic disorder, and agoraphobia are more common in females, but antisocial personality disorder and alcoholism are more common in males. Several physical syndromes that have been reported to be associated with Briquet's syndrome also may be part of this aggregation of disorders, including irritable bowel syndrome (20) and ovarian cysts (19). I call this aggregation of disorders the "Briquet's spectrum." A corollary to the present hypothesis is that the greater the degree of aggregation of Briquet's spectrum disorders seen in a given individual, the greater the likelihood that the individual will

show typical traits of Briquet's syndrome, such as multiple somatic complaints, chronicity, and sickness.

The present hypothesis conceptualizes somatization in dimensional rather than categorical terms. This viewpoint is consistent with previous suggestions that Briquet's syndrome sometimes may occur in a milder form (36). Milder forms of Briquet's syndrome may involve a less complete aggregation of syndromes, differing in degree but not in kind from the aggregation seen in narrowly defined Briquet's syndrome.

According to the present hypothesis, somatization disorder, rather than being categorically distinct from affective and anxiety disorders as suggested by *DSM-III*, actually may be a collection of these and other syndromes aggregated in a complex form involving extensive psychiatric and somatic comorbidity. This hypothesis is consistent with reports of extensive psychiatric comorbidity in somatization disorder (16, 37). It also is consistent with reports of elevated rates of antisocial personality disorder and alcoholism in the relatives of patients with Briquet's syndrome (3). As predicted by the present hypothesis, patients with antisocial personality disorder (38) and alcoholism (39) have been shown to have substantial rates of secondary depression and panic attacks.

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Depression, Hopelessness, and Suicidal Behavior in Chinese and American Psychiatric Patients

John A. Chiles, M.D., Kirk D. Strosahl, Ph.D., Zheng Yan Ping, M.D.,
Mark C. Michael, Ph.D., Kathryn Hall, M.D., Ron Jemelka, Ph.D.,
Brian Senn, B.S., and Cathy Reto, R.N.

The authors compared 37 patients in the People's Republic of China and 46 patients in the United States who were having difficulty with suicidal thinking or behavior. Hopelessness, reasons for living, and suicidal efficacy showed none of the expected relationships with suicidal intent among the Chinese patients, but the two groups were similar on many variables theoretically related to suicidality. Chinese patients were less likely to communicate suicidal intent and rated suicide as less effective at solving problems. The authors examine such variations in the light of possibly different cultural approaches to suicidal behavior.

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In Western medicine, psychiatric illnesses have a well-established link with suicidal behavior. Suicidality is considered a diagnostic feature of depression in DSM-III-R, and suicidal thoughts, suicide attempts, and completed suicides have been associated with a variety of mental disorders, including schizophrenia, alcoholism, and anxiety disorders, and with borderline and antisocial personality disorders. Although the Western psychiatric literature acknowledges the role of social factors in suicidal behavior, the major causal emphases are placed on biological, genetic, and intrapsychic determinants. In the West, a suicidal person is often evaluated for a psychiatric illness, with the assumption that an effective psychosocial and/or psychopharmacological intervention can be applied.

The Chinese perspective of suicide has developed differently from that of the West. For most of Chinese

history, the act of suicide has not been regarded as deviant and has, at times, been encouraged by the state (1). Although pioneers against this attitude can be traced to ancient times, there is scant evidence that suicide has been related to mental illness. Rather, Chinese writers have consistently viewed the genesis of suicide as social rather than medical or psychiatric in nature.

Quite recently, Western diagnostic criteria have been systematically applied to patient populations in the People's Republic of China (2-3), and results suggest that suicidal behavior is associated with psychiatric illness among Chinese patients. Dunner et al. (4) reported that the symptoms, course, and familial factors in Chinese patients with primary affective disorder are similar to findings in equivalent U.S. groups. Interestingly, of 40 Chinese patients diagnosed as suffering from unipolar or bipolar illness in that study, 13 (32.5%) had a history of suicide attempts and 31 (77.5%) gave a history of suicidal thoughts. The 32.5% rate of suicide attempts is within the range of 30%-50% that Stallone et al. (5) reported in American patients with primary affective disorder seen in an outpatient clinic. Thus, suicidal behavior (substantial suicidal ideation and/or deliberate self-harm with some intent to die) was a clinical problem in the Chinese patients studied by Dunner et al. and was at least associated with the presence of a mental disorder. Somatic concerns also play a considerable role in Chinese culture in expressing conditions of distress; indeed, the language itself is much richer in somatic expressions than in affective expressions (6). Kleinman (2) reported that the illness experience of Chinese patients with depression is more somatic than intrapsychic.

Beck et al. (7) have emphasized the importance of depression and hopelessness as causal factors in suicidal behavior. Specifically, their theory states that greater depression and hopelessness are associated with greater suicidal potential and that hopelessness acts as a cognitive mediator of the relationship between depression and suicidal behavior. Thus far, a variety of studies have supported this hypothesis, using such indicators of suicidal potential as intensity of suicidal ideation (7, 8) and suicidal intent ratings obtained after the fact from suicide attempters (9). Else-

Received Dec. 7, 1987; revision received June 27, 1988; accepted Sept. 9, 1988. From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle; the Mental Health Department, Group Health Cooperative of Puget Sound, Seattle; and the Department of Psychiatry, Hunan Medical College, Changsha, People's Republic of China. Address reprint requests to Dr. Chiles, Department of Psychiatry and Behavioral Sciences, ZA-31, University of Washington, 326 Ninth Ave., Seattle, WA 98104.

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where (10, 11) we have suggested that other cognitive processes may play an instrumental role in determining the form and intensity of suicidal behavior. Suicidal behavior may occur not simply because depression and hopelessness are present. Rather, depressed and hopeless individuals often display a variety of dysfunctional coping responses (alcohol and/or drug abuse and social withdrawal, for example) in addition to or rather than suicidal behavior. The global, pessimistic beliefs about one's future that characterize the state of hopelessness are not specifically suicidal in content. Other beliefs, such as attitudes militating against suicide, or evaluations of the problem-solving efficacy of suicide, should also mediate the form and intensity of suicidal behavior (11, 12). The nature of the precipitating problems may also relate to the form of suicidal behavior (13), and the expressed problems may differ cross culturally.

The majority of research pertaining to these theories has been generated by using psychiatric patients from the United States and the United Kingdom. There is scant research using non-Western cultures on the applicability of these theories and, to our knowledge, no studies from within China, whose estimated 1.1 billion people constitute more than 20% of the world's population. The cross-cultural research reported here examines the role of depression, hopelessness, suicide-specific attitudes, and precipitating problems in relation to suicidal ideation and suicide attempts in matched Chinese and American psychiatric samples. Four cross-cultural hypotheses were tested: 1) Precipitating problems for both suicidal ideation and suicide attempts vary, and somatic concerns are more prevalent among the Chinese. 2) The relationship between suicidal behavior and hopelessness remains when depression is controlled for, but not vice versa. 3) Hopelessness is related to suicidal potential to a greater extent than is depression. 4) Suicide-specific beliefs such as attitudes against suicide and evaluation of suicide as an effective problem-solving behavior relate to suicidal behavior.

METHOD

Subjects

For the Chinese sample, 37 patients from the Department of Psychiatry at Hunan Medical College were evaluated. All patients were ethnic Chinese (Han people) and were selected by their Chinese physicians because they were having current difficulty with suicidal thinking and/or recent suicidal behavior. The group consisted of 24 men and 13 women, with a mean age of 29.1 ± 10.9 years. During the same time frame, 122 patients admitted to the psychiatric service at the University of Washington who had current suicidal ideation or behavior were evaluated. From this group, a sample matched for age and sex as closely as possible with the Chinese patients was chosen. The

matched U.S. sample consisted of 46 patients (29 men, 17 women) with a mean age of 30.2 ± 10.4 years. Informed consent was obtained from all patients.

Classification of suicidal behavior was based on responses to certain items in the Suicidal Thinking and Behavior Questionnaire, described later in this paper. Fifteen Chinese patients (10 men, five women) had made a suicide attempt within 3 months of the evaluation, and 22 Chinese patients (14 men, eight women) had current suicidal ideation. In the American sample 19 patients (13 men, six women) had made a suicide attempt within a week of the evaluation, and 27 patients (16 men, 11 women) were admitted with suicidal ideation. There were no significant differences between or within groups in sex or age.

There were unavoidable dissimilarities between the American and Chinese subjects based on culturally determined differences in medical or psychiatric practices. First, the American patients typically made a suicide attempt or expressed suicidal intent, were quickly brought to a physician's office or emergency room, and then hospitalized. Vast differences in the availability of transportation and physicians mean that psychiatric evaluation occurs later in the course of a suicidal event in the People's Republic of China. Second, all American patients were currently hospitalized, but only three of the Chinese patients were currently hospitalized. The rest were treated as outpatients. The inner city of Changsha has approximately 60 acute-care psychiatric beds available for its estimated one million people, and many psychiatric conditions that would be treated through hospitalization in the United States are treated on an outpatient basis. Third, marital status was significantly different in the two groups. Within the American group, 24 patients were currently married, six had never married, 15 were divorced or separated, and one was widowed. Among the Chinese, 19 were married and 18 had never married; there were no divorced, separated, or widowed patients (Yates'-corrected $\chi^2 = 22.15$, $df = 3$, $p < 0.0003$). In the People's Republic of China, divorce and separation are culturally unacceptable and rare. Finally, the American sample, although best described as lower-middle-class, showed more socioeconomic variability than the Chinese sample. More of the American patients were unemployed and had not completed their required public education. School dropouts are rare in the People's Republic of China, and almost everyone is currently employed, often in a community-based work group (*danwei*).

Instruments

Suicidal Intent Scale. The Beck Suicidal Intent Scale (9) is a 15-item research instrument designed to assess the factual aspects of a suicide attempt and the circumstances surrounding it as well as the patient's thoughts and feelings at the time of the attempt. Individual responses are coded on a 0–2 Likert scale; total Suicidal Intent Scale scores can range from 0 (extremely low

intent) to 30 (extremely high intent). A questionnaire version of the Suicidal Intent Scale was used (12). Suicidal intent ratings were used as our criteria for suicidal potential in this study because of the empirically established relationship between the level of suicidal intent and the risk of a subsequent suicide (7).

Reasons for Living Inventory. The Reasons for Living Inventory (14) is a 48-item scale that asks the respondent to rate the importance of various reasons for not committing suicide, if the thought were to occur. Each item is rated on a scale of 1 (not important at all) to 6 (extremely important). Factor analytic research indicates that the Reasons for Living Inventory comprises six subscales: survival and coping beliefs, child-related concerns, family-related concerns, fear of the act of suicide, fear of social disapproval, and moral concerns.

Beck Hopelessness Scale. The Beck Hopelessness Scale (15) is a 20-item true-false questionnaire assessing negative expectations and pessimism about one's future. One-half of the items are reverse-scored. Total scores can range from 0 to 20 and are obtained by summing the individual items.

Beck Depression Inventory. The Beck Depression Inventory (16) is a 21-item inventory that asks the respondent to indicate which of a series of statements best describes how he or she has felt over the last several days. Responses are coded on a 0–3 Likert scale and summed to provide a global depression score. A score of 18 or greater is indicative of clinically significant depression.

Suicidal Thinking and Behavior Questionnaire. This instrument, a refinement of one used earlier in our research (11), consists of questions about suicidal ideation, suicide attempts, life problems associated with suicidality, and knowledge about suicidal behavior in significant others. The Suicidal Thinking and Behavior Questionnaire also has an item that asks the respondent to rate the efficacy of suicidal behavior on a 1–5 scale on which 1=suicide not effective at all in solving problems and 5=suicide completely effective at solving problems.

All instruments were translated from English to Chinese by one of us (Z.Y.P.), and the accuracy of the translations was reviewed and approved by bilingual senior Chinese clinicians.

Procedure

American patients were selected from consecutive daily admissions to two psychiatric units at University Hospital, Seattle. Initial determination of a suicide attempt or serious suicidal ideation was made by review of admission logs and chart notes. Patients with acute thought disorders, organic brain syndrome, or drug and/or alcohol intoxication were excluded from participation. Patients with suicide attempts or suicidal ideation were then contacted by research assistants and asked to complete a battery of questionnaires that included the instruments already described. The bat-

tery took approximately 2 hours to complete, and ordinarily patients did it in the evening hours after completion of their daily ward routine. A patient's status as a suicide attempter or suicide ideator was confirmed by comparing his or her responses on the Suicidal Thinking and Behavior Questionnaire with admission and chart entries. Patients completed the study instruments within 5 days of hospital admission.

Chinese patients were selected by their physicians from the outpatient and inpatient psychiatric programs at the Hunan Medical College because of current suicidal ideation and/or recent suicidal behavior. Exclusion criteria were the same as for the American patients, as was the battery of tests. In all cases the battery was completed on the day the patient was referred to two of us (J.A.C. and Z.Y.P.) and took about 2 hours. Each patient's suicidal status was confirmed by comparing Suicidal Thinking and Behavior Questionnaire items and chart entries.

RESULTS

Differences Between American and Chinese Suicidal Patients

The American sample reported first thinking of suicide at a significantly earlier age than the Chinese: the mean \pm SD age for the American sample was 21.4 ± 7.99 years and that for the Chinese sample was 26.1 ± 10.84 years (two-tailed $t=-2.22$, $df=80$, $p<0.05$). American patients were more likely than Chinese patients to experience increasing intensity of suicidal ideation from its inception to the index study contact (two-tailed $t=5.29$, $df=78$, $p<0.01$). American patients reported more previous suicide attempts than their Chinese counterparts (two-tailed $t=4.67$, $df=81$, $p<0.001$). No Chinese patients reported deliberate self-injury without suicidal intent, but a number of Americans did so (American mean= 1.41 ± 3.59 times). The Americans were much more likely to have communicated their suicidal intent to someone in their social support system ($N=39$, or 84%) than were the Chinese ($N=10$, or 27%) (Yates'-corrected $\chi^2=25.27$, $df=1$, $p<0.0001$). Table 1 lists the mean scores on the suicide instruments of each group.

Univariate 2×2 analyses of variance (Chinese ideators and attempters versus American ideators and attempters) were conducted on the depression, hopelessness, suicidal efficacy, and reasons for living inventories. Results on the Reasons for Living Inventory fear of social disapproval subscale indicated that social disapproval was a more important reason for not committing suicide by the Chinese than by the Americans ($F=7.21$, $df=1$, 79 , $p<0.01$). American patients rated suicide as significantly more effective as a problem-solving behavior than did Chinese patients ($F=6.25$, $df=1$, 79 , $p<0.01$). The difference between the two groups in depression levels narrowly failed to

TABLE 1. Suicide Inventory Scores of 46 American and 37 Chinese Suicidal Patients

Inventory	Score of American Patients				Score of Chinese Patients				Total (N=83)	
	Suicidal Ideation (N=27)		Suicide Attempt (N=19)		Suicidal Ideation (N=22)		Suicide Attempt (N=15)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Beck Depression Inventory ^a	24.3	10.6	19.6	12.2	15.5	9.7	19.6	12.6	19.7	11.1
Beck Hopelessness Scale ^a	11.7	5.4	7.6	6.8	9.4	4.7	10.0	4.9	9.7	5.1
Suicide efficacy rating	3.5	1.8	2.8	1.9	2.5	1.5	2.0	1.5	2.8	1.7
Reasons for Living Inventory										
Survival and coping beliefs	2.1	2.3	3.3	2.2	3.3	1.7	3.4	2.0	2.9	2.1
Family-related concerns	2.4	2.4	3.3	2.3	3.5	1.8	3.7	2.0	3.1	2.2
Child-related concerns	1.0	2.2	2.2	2.6	3.1	2.5	2.9	2.3	2.1	2.2
Fear of social disapproval	1.3	2.0	2.0	2.1	2.9	1.7	2.5	1.9	2.1	2.0
Moral concerns	1.3	2.0	1.5	1.7	1.9	1.2	2.4	1.6	1.7	1.7
Fear of the act of suicide	1.8	2.0	2.0	1.8	2.1	1.4	2.2	1.8	2.0	1.7

^aScores are missing for eight patients: Five American ideators, one American attempter, and two Chinese ideators.

TABLE 2. Life Problems Preceding Suicide Attempt or Ideation of 41 American and 28 Chinese Suicidal Patients

Life Problem	Suicide Attempters ^a				Suicide Ideators ^b				Total ^c			
	American (N=15)		Chinese (N=10)		American (N=26)		Chinese (N=18)		American (N=41)		Chinese (N=28)	
	N	%	N	%	N	%	N	%	N	%	N	%
Problems with significant others	9	60	2	20	13	50	1	6	22	54	3	11
Problems with social adjustment	1	7	1	10	2	8	5	28	3	7	6	21
Physical problems	0	0	5	50	2	8	9	50	2	5	14	50
Emotional distress	5	33	2	20	9	35	3	17	14	34	5	18

^a $\chi^2=10.15$, $df=3$, $p=0.017$.

^b $\chi^2=18.17$, $df=3$, $p=0.000$.

^c $\chi^2=27.22$, $df=3$, $p=0.000$.

achieve significance ($F=3.41$, $df=1$, 71 , $p<0.07$); the depression level of the American sample was higher. A nonsignificant trend was also noted for the Reasons for Living Inventory moral concerns subscale: Chinese patients tended to rate this higher as a reason for not committing suicide ($F=3.64$, $df=1$, 79 , $p<0.10$). Interestingly, no differences were noted on the Reasons for Living child-related concerns scale, a factor that would seem likely to be of great importance to Chinese patients. No significant differences were observed between American and Chinese patients in level of hopelessness or suicidal intent (suicide attempter groups only). Suicide attempters did not differ from suicide ideators on any of the research measures. This was true for both samples.

Problems Precipitating Suicidal Behavior

To examine the study hypothesis regarding precipitating events, a content analysis was performed on responses from suicide ideators and attempters regarding the immediate life problem that helped precipitate suicidal behavior. Originally, responses were independently sorted by two of us (J.A.C. and K.D.S.) into 10 distinct categories; our agreement rate was 100%. Approximately 20% of these responses occurred with insufficient frequency to permit any meaningful statistical analysis and so were excluded. Responses were

then placed in one of four reliable categories: problems with significant others (friends, family, and spouses), problems with social adjustment (work or school), physical problems, and emotional distress (anxious and/or depressed states). Table 2 presents the results of Yates'-corrected chi-square analyses using the Bonferroni alpha level correction ($p=0.017$) in a comparison of suicide attempters and suicide ideators. As can be seen, Chinese patients as a group were more likely than American patients to report physical health concerns as reasons for initiating suicidal behavior, but American patients reported problems with significant others more frequently than their Chinese counterparts. These somatic concerns were important to both Chinese attempters and ideators, but problems with social adjustment were more important in the Chinese ideator group.

Depression, Hopelessness, Suicidal Expectancies, and Suicidal Intent

Partial correlations were conducted in each sample to determine the relationship between depression, hopelessness, and suicidal intent. In the American sample, the partial correlation between suicidal intent and hopelessness with depression partialled out was $r=0.49$, $df=18$, $p<0.05$; between suicidal intent and depression with hopelessness partialled out it was $r=-0.12$, n.s. However, an opposite pattern was ob-

TABLE 3. Summary of Regression Analyses in 16 American and 15 Chinese Patients Who Attempted Suicide

Item	R	R ² Change	Beta	F Change
Analysis of depression and hopelessness				
American attempters				
Hopelessness	0.60	0.40	0.56	9.54 ^a
Depression	0.49	0.01	0.09	0.10
Chinese attempters				
Depression	0.46	0.21	0.59	3.55 ^b
Hopelessness	-0.04	0.07	-0.30	1.24
Best-fit analysis of suicide efficacy, hopelessness, and depression				
American attempters				
Suicide efficacy rating	0.73	0.53	0.51	16.07 ^c
Hopelessness	0.60	0.08	0.36	2.92
Chinese attempters				
Depression	0.46	0.21	0.55	3.55 ^d
Suicide efficacy rating	-0.39	0.24	-0.30	5.29 ^e

^adf=1, 14, $p<0.01$.^bdf=1, 13, $p<0.08$.^cdf=1, 14, $p<0.01$.^ddf=1, 13, $p<0.08$.^edf=2, 12, $p<0.05$.

served in the Chinese sample. The partial correlation between suicidal intent and hopelessness with depression partialled out was $r=-0.27$, $df=13$, n.s.; between suicidal intent and depression with hopelessness partialled out it was $r=0.54$, $df=13$, $p<0.05$. In contrast to our predictions, the partial correlational relationship between depression and hopelessness in Chinese attempters was the opposite of that noted in American attempters. Interestingly, hopelessness and depression correlated positively with one another in the overall Chinese sample ($r=0.32$, $df=35$, $p<0.05$) but at a much lower level than in the American sample ($r=0.74$, $df=36$, $p<0.01$).

To test the study hypotheses regarding the relationship between depression, hopelessness, suicide-specific beliefs, and suicidal intent, a forced-entry regression analysis was performed separately for American and Chinese attempters. In this procedure, depression and hopelessness were entered as a variable set, and each variable was tested separately according to its contribution toward the prediction variance accounted for. Results are summarized in table 3. In the American attempter group, hopelessness emerged as a significant predictor of suicidal intent. Depression did not add significantly to the observed prediction effect, a finding consistent with those of previous studies. Inspection of results in Chinese attempters indicated that depression predicted suicidal intent among Chinese patients but at a marginal level of significance, and hopelessness did not add significantly to the observed effect.

A second series of focused regression analyses were conducted to identify "best fit" solutions in the prediction of suicidal intent for American and Chinese attempters. This analysis included the results presented in table 3. As can be seen, depression and the suicide

efficacy rating combined to produce a strong prediction effect in Chinese attempters ($F=5.29$, $df=2$, 12 , $p<0.02$). Depression exhibited a positive linear association (higher depression led to greater intent), but suicide efficacy bore a negative relationship (higher intent led to lower ratings of efficacy). Overall, this two-variable system accounted for 45% of the variation in suicidal intent scores. Among American attempters, suicide efficacy and hopelessness produced a strong prediction effect ($F=10.60$, $df=2$, 13 , $p<0.01$). Both hopelessness and suicide efficacy levels showed a positive relationship with suicidal intent. Overall, 61% of the prediction variance was accounted for, the majority attributable to the suicide efficacy rating.

A discriminant function analysis was performed on the American and Chinese attempter groups to determine which linear combination of variables best distinguished the two groups. Results indicated that a significant discriminant function was derived when suicide efficacy and hopelessness were entered (Wilks' $\lambda=0.77$, equivalent $F=4.21$, $df=2$, 29 , $p<0.02$). A classification analysis indicated that these two predictors correctly identified 73% of the American attempters but only 54% of the Chinese attempters (no better than chance accuracy). The lack of classification accuracy with Chinese patients is probably due to an "averaging" effect produced by the suicide efficacy rating and the fact that hopelessness exhibited a near-zero-order relationship with suicidal intent scores among Chinese patients.

DISCUSSION

Results of this study suggest that there are many similarities between American and Chinese suicidal patients in personality variables that are theoretically related to suicidal behavior (i.e., depression, hopelessness, reasons for living). In general, both groups of patients reported high levels of depression and hopelessness and fewer reasons for living. However, there are also intriguing differences between these groups that are worthy of further study.

The Chinese patients in this study reported a decrease in suicidal ideation after its inception, rated suicide as less effective in solving problems, were less likely to communicate suicidal intent to others, and made fewer suicide attempts. Why is this? The answer may be partially found in the way suicidal behavior is handled in the two cultures. The American patients in this study were taken to a hospital out of concern for their personal welfare and to allow them to be evaluated and treated. The reaction of their social support network was likely to have been one of concern and helpfulness, a positive change in what the patient was likely to have perceived as a hostile and unloving environment. In short, the behavior worked, and the suicide attempt was consequently evaluated as an effective problem-solving device (i.e., reinforced).

It is much less likely that the Chinese patients expe-

rienced a concerned, supportive, and thus reinforcing reaction to their suicidality. Suicidal behavior tends to be seen less as a symptom of illness or psychological distress and more as a condition that brings embarrassment and shame to one's family and, to a lesser extent, to one's work group. Medical help may not be as actively sought and is not readily available in many cases. The immediate consequence of a suicide attempt is likely to be stern discussions with the support group, with the emphasis on, "You must stop this," rather than, "Now that we recognize your pain, how can we help you?"

Hopelessness, reasons for living, and suicidal efficacy showed none of the relationships with suicidal intent in the Chinese sample that one typically observes in American patients and, in fact, were obtained in this American sample. The significant negative correlation with the efficacy rating suggests that after a suicide attempt, the more suicidal intent a patient describes the less efficacy he or she ascribes to the behavior. By Western standards, this might describe the desired outcome of an effective clinical intervention.

The relationship between depression, hopelessness, and suicidal intent may be quite different for Chinese and American patients. Depression, not hopelessness, was related to suicidal intent in the Chinese patients. The connection between hopelessness and intent may not have been valid for this Chinese sample, possibly because hopelessness is buffered by cultural or moral experiences and beliefs. The Chinese perspective on "the way life is" may involve a more enduring attitude toward personal loss or privation, lack of individual control over aversive events, and a subjugation of individual needs to the needs of one's immediate community. It is only with the advent of major affective disturbance and somatic concerns that a Chinese person perceives the situation to be a "problem" requiring more extreme problem-solving behavior.

These data also raise a question concerning the universality of a structural relationship between depression, hopelessness, and suicidality. If one culture shows no such relationship, might others also fail to show it? Further work in this area would be of both theoretical and psychotherapeutic interest.

Caution is needed in interpreting the results of this study. It was a pilot venture, done over a short period of time at two specific sites. A more complete design would include controls for culturally determined differences in diagnostic practices and environmental stress levels as well as a control group of nonsuicidal Chinese patients. Subtle differences in the translated versions of each scale may have skewed the results. We feel, however, that the review by senior bilingual Chinese clinicians was effective and that the group differences, especially those involving depression, hopelessness, and intent, produced theoretically understandable patterns that were unlikely to be the result of chance factors.

Control for number of children would also be useful. Given the well-known strength of family ties

among the Chinese, we were surprised at the nonsignificant difference on the child-related concerns subscale of the Reasons for Living Inventory. The fact that 93% of the American patients were or had been married but only 49% of the Chinese patients were married probably influenced these results. Finally, the time lapse between occurrence of the target suicidal behavior and data collection was something we were unable to control, especially among the Chinese patients.

The consistent differences in these results, however, should provoke interest in further cross-cultural studies with the People's Republic of China, particularly studies of the Chinese approach to the suicidal patient. Such studies might reveal new principles to follow in treating these common, costly, and difficult-to-manage behaviors. Additionally, these results may have possible utility for American psychiatrists working with Asian immigrant populations. Hopelessness may now be a critical variable to address in the treatment of suicidality in some of these individuals.

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Financing the Medical Management of Mental Disorders

Steven S. Sharfstein, M.D., and Howard Goldman, M.D., Ph.D.

In 1987 Medicare benefits for the mentally ill were expanded for the first time in 22 years. A major change was the removal of limits and copayments for the "medical management of psychopharmacologic agents." Payment for medical management recognizes the trend toward the remedicalization of psychiatry; however, medical management can be defined either broadly or narrowly. The authors suggest pricing strategies for both medical management of mental disorders and psychotherapy. Enlightened design of psychiatric benefits will cover all forms of treatment according to appropriate rules. Access to treatment for mental illness is at stake as these rules develop.

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At the very end of the first session of the 100th Congress in December 1987, the Congress expanded the outpatient psychiatric benefit in Medicare. Ironically, in a bill devoted to deficit reduction and reconciliation of the budget (the Omnibus Budget Reconciliation Act of 1987), the Medicare benefit for treatment of "mental, psychoneurotic, or personality disorder" was increased for the first time in 22 years.

Since its inception in 1965, Medicare had covered only \$500 per year of psychiatric treatment services provided outside a hospital inpatient setting; the effective copayment was 50%, resulting in a maximum payment by Medicare of \$250 per year. No distinctions were made for different types of outpatient treatment, and alternatives to hospitalization, such as partial hospitalization, were not covered by a statutory benefit. The new law has three provisions: the outpa-

tient benefit will be increased in two stages over 2 years to \$2,200 annually (with a 50% copayment); partial hospitalization is established as a reimbursable service subject to government regulations to be developed; and all limits and special copayments are removed from the "medical management of psychopharmacologic agents" for Medicare beneficiaries. This type of medical management is to be covered on a par with the outpatient treatment of all other medical illnesses, that is, with an 80%-20% copayment and no visit or dollar limits. But what is medical management?

Medical management is a controversial concept. Skeptics view it as a prelude to eliminating insurance coverage for psychotherapy and fear that it will encourage unnecessary drug treatment and create an incentive to diminish the time spent talking to patients. Proponents argue that this new policy distinguishes between types of outpatient treatment and provides appropriate, varying coverage for all of them, including a substantial increase in what is essentially a psychotherapy benefit. This report explores the meaning of medical management and its implication for psychiatric treatment and financing the care of the mentally ill.

Statutory language referring to the "medical management of psychopharmacologic agents" reflects a narrowing of a broader concept of medical management that had been suggested by earlier uses of the term by Medicare and that had been recommended by the American Psychiatric Association. The actual meaning of the term will require regulatory definition, followed by instructions from the Health Care Financing Administration to its Medicare fiscal intermediaries and carriers. At this juncture we wish to discuss the antecedents of this change in financing policy, offering a range of definitions of medical management.

HISTORICAL REVIEW

The predominant role of psychotherapy in American psychiatry is a relatively recent phenomenon that ex-

Received Mar. 14, 1988; revision received Aug. 15, 1988; accepted Sept. 9, 1988. From the Sheppard and Enoch Pratt Hospital and the University of Maryland School of Medicine, Baltimore. Address reprint requests to Dr. Sharfstein, Sheppard and Enoch Pratt Hospital, 6501 North Charles St., P.O. Box 6815, Baltimore, MD 21285-6815.

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tends back no more than 40 years. The long-standing role of physicians in the care of the mentally ill was the management of the medical problems of these patients, who were confined in separate hospitals or in undifferentiated welfare institutions (poorhouses), often for the purpose of segregation rather than treatment. It was only in the late eighteenth century that the idea of mental illness as definable disease for which physicians could give specific treatments came about. Physicians who were called upon to treat the medical problems of the insane became interested in the treatment of insanity itself. Benjamin Rush, the father of American psychiatry, was such a physician. The original Association of *Medical Superintendents*, the first medical specialty society in the United States, represented a shift of interest as well as movement to specialty hospitals.

In the early nineteenth century, when families and local charitable organizations became unable to bear the entire financial burden of the care of the mentally ill, the states assisted them by building and staffing asylums. Psychiatric care throughout the latter half of the nineteenth century took the form of medical/neurological diagnosis, somatic interventions, and custodial care. Local governments remained financially responsible for each episode of care until passage of state care acts at the turn of the century shifted the total cost of the care of the indigent mentally ill onto the state (1-3).

Early in the twentieth century, the revolution of psychoanalysis and the mental hygiene movement introduced psychotherapy as a promising intervention for the miseries of the mentally ill. Talking therapies became the predominant treatment in the era before effective pharmacotherapy. Before the introduction of third-party payment, paying for treatment involved a case-by-case arrangement between the doctor and the patient. In contrast, between 1940 and 1970 the financing and pricing of psychotherapy became the concern of public and private insurers. Dollar and visit limits were coupled with separate deductibles and higher copayment schedules to curb anticipated overutilization. The treatment hour became the reimbursable unit, and this had a profound impact on the definition of the psychiatric task and the nature of psychiatric practice. It also was the determining factor in the income of psychiatrists, especially in the early 1970s, when psychiatry dramatically lost ground to other medical specialties in median net income as well as in numbers of American medical graduates choosing psychiatry as a specialty (4, 5).

Poor and discriminatory private third-party coverage persists. Medicare in 1965 paid a maximum of only \$250 a year in reimbursement for outpatient psychiatric treatment, and private third-party insurance almost universally discriminated against the "functional illness" represented by the major mental disorders, including schizophrenia, bipolar disorders, the neuroses, and personality disorders. Reimbursement was considered more legitimate for biomedical treatments and procedures for organic disorders, and third-

party insurance's bias toward procedures continued especially in the Medicare program and in most private third-party health insurance plans. Beginning in the mid-1970s, psychiatry became "remedicalized," an inpatient treatment of severe mental illness began to closely resemble the inpatient treatment of most medical illness. Shortened hospital stays, the prescription of a variety of antipsychotic, antidepressant, and anti-anxiety medications, the revival and effective use of ECT, and the rebirth of reliable psychiatric diagnosis through the publication of *DSM-III* and *DSM-III-R* have further moved the field toward its medical base.

SEEKING A POLICY OF PARITY

Advocates for improved insurance coverage of services for the mentally ill have sought "parity" of that coverage with the benefits for general health service. (6). Parity implies that comparable services are comparably covered by insurance policies regardless of the patient's diagnosis. Historically, insurance benefits for the treatment of mental disorders have been limited because of concern about moral hazard, overutilization, and uncontrolled costs (7). All ambulatory mental health care was viewed as long-term psychotherapy, and the diversity of practice was never recognized (8). Recently, the concern has been reinforced by research findings which suggest that the demand for mental health services is more responsive to the lowering of price brought about by insurance coverage than is the demand for general medical services (9, 10). Although it has been suggested that some services (e.g., psychotherapy) might be more price responsive than others (e.g., psychoeducational services), benefit design generally subjects all ambulatory services to the same limits, in the form of higher deductibles, copayments, and lower charge and visit maximums (11). Only very recently has there been a change in this approach to the design of psychiatric benefits.

In September 1984, the Department of Health and Human Services issued a report on Alzheimer's disease. The department announced a change in Medicare coverage that removed limitations on services provided to patients with Alzheimer's disease, an organic medical and mental condition that is listed not only in the psychiatric code but also with a neurologic disease code in *ICD-9*. The recommendation of the task force stated, "The current Medicare statute limits medically appropriate physician services provided outside of the hospital setting for patients with Alzheimer's disease when coded as a mental disorder. The Department should clarify that, except for psychotherapy, physician treatment services for patients with Alzheimer's disease and related disorders are not subject to the \$250 limitations. In other words, in determining whether services for these patients are subject to the limit, the nature of the physician's service is the deciding factor, not the diagnostic code. Therefore, physician treatment services provided outside the hospital

etting for patients with Alzheimer's disease and related disorders coded 290.X (in *DSM-III* and *ICD-9*) should be reimbursed in the same manner as services for Alzheimer's disease coded 331 (*ICD-9*)" (12).

This change was put into place by the Department of Health and Human Services and led to a recommendation in the Congress that any limits on the medical management of mental disorders outside the hospital setting be eliminated. It is here that the emphasis on parity of reimbursement for the treatment of mental disorders and general medical conditions means equal pay for similar work. Procedures for the medical management of diabetes, arthritis, and schizophrenia are similar in many ways. Such similar procedures should not have different copayments or deductibles or separate limits. In contrast, psychotherapy is a specific procedure, and there is no comparable treatment entity in the *Current Procedural Terminology* (CPT) manual.

Furthermore, as we have noted, psychotherapy is regarded as having special economic demand properties.

The Alzheimer's disease task force recognized this distinction in its policy recommendation. The new financing policy proposed separate limits and copayments for a specific treatment (i.e., psychotherapy) but proposed parity for medical management, a form of intervention and treatment focused on the severely ill, especially those with organic mental disorders.

DEFINING MEDICAL MANAGEMENT

Medical management of mental disorders consists of diagnosis and treatment provided by a physician or under a physician's supervision. Psychotherapy may be considered one element of medical management and, as such, should be included in the definition, with the understanding that there may be financial limits on this specific procedure.

Medical management is primarily cognitive in nature, although many of the laboratory tests used in monitoring the treatment of mental disorders are beginning to shift psychiatry into a more procedural mode similar to that of internal medicine and neurology. The monitoring of serum levels of various drugs, brain scans, and other medical tests empower the psychiatrist to become the medical manager as well as a provider of specialized therapeutic care. For example, the medical management of bipolar disorder requires a careful history to help establish the diagnosis, as well as appropriate physical examination and laboratory tests. A trial of lithium and/or perhaps other medications, monitoring the blood level of these medications, careful counseling of the patient and the family in the use of these medications, and the identification of early symptoms of relapse make the management of this illness quite similar to the management of diabetes or arthritis. In times of severe or acute distress or disability, hospitalization is warranted, and long-term medical management would take place outside the hospital setting.

Medical management has been more narrowly defined by the current legislation. Restricting the concept to medical management of psychopharmacologic agents simplifies it and satisfies the interests of legislators and budget guardians in creating a limited benefit that conforms to basic medical practice. Although the restriction was a necessary compromise to retain the principle of parity (80% copayments with no annual limit on charges or visits) for some outpatient psychiatric treatments in Medicare, the narrow definition may oversimplify the concept of medical management and could pose a number of problems for policy and practice.

The narrowest definition of drug management might require that a prescription be written during the course of an office visit in order to qualify for the special benefit. Although compliance with the requirement would be verifiable, such an operational definition would invite "gaming" (i.e., altering accepted clinical practice to conform to the benefit rules) or, worse, might encourage the unnecessary use of medications, especially when they are only marginally indicated. A somewhat broader definition might require only that a prescription be written at some point or that issues of dosage, effect, and complications be discussed or be assessed through an examination of the patient. This definition, too, could invite gaming and overutilization of services. Any definition of drug management is likely to imply brevity of contact between the physician and the patient. Parity is likely to be available only for drug management or for low-cost services, such as brief encounters in the office setting. More complicated or longer clinical encounters might be envisioned as extended office visits, special diagnostic procedures, or psychotherapy visits (even when medication is prescribed).

If the basic concept of the policy change implies paying for those aspects of psychiatric practice that conform to general medical practice, then the new legislation represents an important precedent, but it is perhaps limited. A fiscally responsible and clinically reasonable alternative could be developed that conforms to common principles of health insurance.

A PRICING AND CODING ALTERNATIVE

In general medical practice, the office visit is the basic unit of outpatient service and ambulatory health care financing. Typically, these services are paid for without specific limits on annual charges or the frequency or number of visits. Special procedures are paid for according to separate benefit rules. Although it is the predominant service unit in much of psychiatric practice, the psychotherapy hour is a special procedure and not an undifferentiated office visit. As such, a psychotherapy hour is priced at a level above that for the average office visit of comparable length and is subject to special limitations. A complete discussion of the pros and cons of the special pricing of psychotherapy is beyond the scope of this paper. Because of concerns

about overutilization, costs, and the supply of nonphysician psychotherapists, a policy of parity that includes unlimited psychotherapy seems unlikely in the near future, but this does not preclude a policy of insurance parity for office visits by patients with mental disorders for medical management by physicians. The secret is balancing the dual concerns of improving access and controlling the increased costs.

An effective pricing strategy should consider ways to avoid the gaming ploy of calling a psychotherapy visit an office visit to take advantage of an insurance copayment rate of 80% rather than a 50% rate for psychotherapy. The pricing schedule could probably be designed to remove the incentive to misidentify services. The patient and the payer (Medicare, for example) do not want to be placed at a financial disadvantage by calling a psychotherapy visit an office visit. One mechanism would be to price an office visit at something less than 62.5% of the price of a comparable unit of psychotherapy. For example, if an hour of psychotherapy is billed at \$100 with a 50% copayment, the patient pays \$50 and Medicare pays \$50. If the same hour of psychotherapy is called an office visit and the charge is allowed at \$100 with an 80% copayment, the patient pays \$20 and Medicare pays \$80. If, on the other hand, the highest allowable charge for the office visit is \$62.50, then Medicare's liability is limited to \$50 (80% of the charge) and the patient pays only \$12.50. Pricing an office visit so that there is a lower out-of-pocket expense controls the payer's cost but decreases the physician's fee for the visit. However, if office visits lasted only 20–30 minutes, this would increase the physician's hourly reimbursement. It would also increase access to care and might increase the volume of care when coupled with a policy of placing no special dollar or visit limits on office visits for the medical management of patients with mental disorders. In the effort to control costs, an office visit for medical management could be limited to 20 or 30 minutes, which would further discourage gaming. In addition, annual limits on visits might be imposed to control overutilization of all medical care, but we believe that limits, if imposed, should be applied to *all* visits, regardless of the somatic or psychiatric reasons for the visits. Peer review of *all* high levels of use might be instituted, rather than imposing an absolute limit on visits.

Critics of the policy of separate payment rules for medical management and psychotherapy have several legitimate concerns. It is possible that the new balance in incentives will increase the use of biomedical techniques, especially the use of psychopharmacologic agents. It may also decrease the amount of time that physicians spend talking to patients. If the former situation brings needed treatment to psychiatric patients, however, then the new policy is to be praised rather than feared. This is especially true for patients with severe mental impairments, for whom pharmacotherapy is so critical. Chronic patients have had their access to care restricted by earlier policies that sought to control psychotherapy and medical management with

identical reimbursement rules. If the new policy lead to an inappropriate reduction in the amount of time spent with patients, however, then the policy must be reconsidered.

We support the distinction between psychotherapy and medical management because, as currently designed, the separate financing of each actually increases the coverage of both forms of treatment. It would be naive, however, to assume that this will always be the case. We acknowledge that the separation may make psychotherapy more vulnerable to future redesign and reduction of benefits. On the other hand, for the last four decades, psychotherapy has been the mainstay of psychiatric services covered by insurance. As long as psychotherapy is a valued treatment, psychotherapy coverage will be demanded by insurance beneficiaries. After all, third parties are not health care designers by intent; they finance the care that their beneficiaries demand. They cover only "insurable risks," however, shying away from services that are subject to moral hazard, i.e., overutilization stimulated by generous benefits. They will cover services when use can be controlled and when the decision to use care has not been made at the time of enrollment in the insurance plan. The central question seems to be, Is this a benefit that everyone in the risk pool should finance through premiums or taxes, even though only some will use the services?

As we have noted elsewhere (13), the natural compatibility between psychiatric practice and general medical practice enhances opportunities for third-party coverage of the care of individuals with mental disorders. Medical management is a construct that reflects this compatibility. It is a generic concept that distinguishes certain types of psychiatric care from psychotherapy, in particular, in an effort to differentiate psychiatric practices for the purpose of financing care. Enlightened design of benefits will cover all forms of treatment with appropriate rules. In the meantime, we psychiatrists, as specialists, must apply ourselves to defining clearly and specifically our professional activities. Current efforts to modify the CPT codes and to find appropriate values for these services, such as the study to develop a resource-related relative value scale for psychiatry, should be supported. We have a special opportunity to shape our financial destiny. It is our hope that we can do so according to established health insurance principles, providing access to needed care balanced by concern about overutilization. This should serve the mutual interests of society, the profession, and our patients.

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Depression and Alzheimer's Disease

Barry W. Rovner, M.D., Jeremy Broadhead, M.B.B.S., Miriam Spencer, B.A.,
Kathryn Carson, B.A., and Marshal F. Folstein, M.D.

In his classic case, Alzheimer described cognitive symptoms such as amnesia, aphasia, and apraxia and noncognitive symptoms such as delusions and agitation. Recent studies have suggested that depression also occurs in Alzheimer's disease. In this study, 144 patients who met criteria for Alzheimer's disease were examined for depression on a modified version of the Present State Examination. The prevalence rate of major depression was 17%. The depressed Alzheimer's disease patients were more cognitively impaired and more disabled than the nondepressed patients. Studies are needed to clarify the etiology and treatment of depression in Alzheimer's disease.

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Alzheimer (1) described cognitive symptoms of amnesia, aphasia, and apraxia as well as noncognitive symptoms of delusions and agitation in a 51-year-old woman. The cognitive symptoms have been used in the diagnostic criteria for Alzheimer's disease and have been related to neuropathology (2–4). The noncognitive symptoms are less well understood. Study of these symptoms might improve differential diagnosis and treatment of Alzheimer's disease and might indicate subtypes of the disease related to specific neuropath-

ological structures or neurochemical abnormalities (5, 6).

Depression is one noncognitive symptom known to occur in Alzheimer's disease, although its reported prevalence varies from 0% to more than 50% (7–11). It is likely that this wide variation results from the application of a variety of diagnostic methods and criteria.

We examined a large group of patients with Alzheimer's disease who had been referred to an Alzheimer's disease research clinic; clinical criteria were used for the diagnosis of Alzheimer's disease and major depression. We report the prevalence of major depression in this sample and describe new associations of depression, cognition, and disability that emphasize the importance of understanding the mechanism and treatment of depression in Alzheimer's disease.

METHOD

The sample consisted of 144 consecutive outpatients referred to the Johns Hopkins Alzheimer's Disease Research Center from July 1985 to October 1986 who met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (2) for probable (88%) or possible (12%) Alzheimer's disease. All 144 patients also met the DSM-III-R criteria for primary degenerative dementia.

A technician (M.S.) used a semistructured method to obtain from each patient a detailed history of the onset of dementia, its workup, current and past medical problems, current medications, and past psychiatric history. Dependency in activities of daily living was quantified by using the Psychogeriatric Dependency Rating Scales (12), and cognitive impairment was quantified by using the Mini-Mental State examination (13).

A psychiatrist (B.W.R.), blind to past psychiatric history and current medication status, interviewed each patient and a close family member using a mod-

Received April 18, 1988; revision received Aug. 18, 1988; accepted Sept. 9, 1988. From the Departments of Psychiatry and Behavioral Sciences and Neurology and the Dementia Research Clinic, Johns Hopkins University School of Medicine. Address reprint requests to Dr. Rovner, Osler 320, Johns Hopkins Hospital, 600 North Wolfe St., Baltimore, MD 21205.

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TABLE 1. Characteristics of Alzheimer's Disease Patients With and Without Major Depression

Variable	Patients With Major Depression (N=24)				Patients With No Depression (N=120)				Analysis		
	N	%	Mean	SD	N	%	Mean	SD	Test Value	df	p
Sex									$\chi^2=0.1$	1	n.s.
Male	8	33			44	37					
Female	16	67			76	63					
Age (years)			66.5	6.5			69.9	8.1	$t=1.9$	142	n.s.
Age at onset (years)			63.3	6.7			66.1	8.2	$t=1.6$	142	n.s.
Duration of illness (years)			3.3	1.8			3.8	2.3	$t=1.0$	142	n.s.
Score on Mini-Mental State examination			9.5	6.7			13.3	6.4	$t=2.6$	142	0.01
Score on Psychogeriatric Dependency Rating Scales			10.8	7.7			6.1	6.2	$t=-3.2$	136	0.002
Taking psychotropic medications	20	83			44	37			$\chi^2=17.6$	1	0.0001
Past psychiatric history	7	29			8	7			$\chi^2=10.9$	1	0.001
Other medical problems	17	71			82	68			$\chi^2=0.06$	1	n.s.

modified version (14) of the Present State Examination (PSE) (15). The reliability and validity of this modified instrument have previously been reported for patients with stroke and dementia (14). The diagnosis of major depression was based on *DSM-III-R* criteria with symptoms elicited from the modified PSE. We used major depression as the diagnosis rather than primary degenerative dementia with depression because the latter lacks specific diagnostic criteria for depression.

To assess interrater agreement, 14 consecutive patients (10%) from the sample and their families were examined by two psychiatrists (B.W.R. and J.B.). Both were present at all 14 interviews, and both simultaneously recorded all symptoms elicited by the modified PSE. The psychiatrists then independently decided whether each patient met the *DSM-III-R* criteria for major depression. Of the 14 patients, three were found by both psychiatrists to meet these criteria, and in no case was there disagreement regarding either the presence or absence of major depression.

The statistical methods employed in this study included two-tailed *t* tests and chi-square comparisons of depressed and nondepressed patients.

RESULTS

The demographic characteristics of the sample (N=144) were similar to those reported by investigators in two other Alzheimer's disease research centers (16, 17). A total of 24 patients (17%) met the *DSM-III-R* criteria for major depression.

Table 1 shows the clinical characteristics of the depressed and nondepressed patients. Depressed patients were more cognitively impaired and more disabled in activities of daily living, but they were no more likely to have other medical conditions that might have contributed to these impairments. Depressed patients were also more likely to be receiving treatment with psychotropic medications and were more likely to have histories of psychiatric disorder before the onset of dementia.

DISCUSSION

Previous studies on the prevalence of depression in Alzheimer's disease have been difficult to interpret because of differences in patient samples, methods of study, and diagnostic criteria. Miller (7) used the Hamilton Rating Scale for Depression to study a diagnostically heterogeneous group of demented patients and found that depressive symptoms occurred more frequently in demented than in nondemented subjects. Lazarus et al. (8) and Knesevich et al. (9) studied patients with well-defined Alzheimer's disease, but they, like Miller, used the Hamilton scale to identify depressive symptoms and found conflicting results. None of these studies reported a prevalence rate for major depression. Reifler et al. (10) reported a prevalence rate of 23%, which is similar to the 17% we report, yet they, like Miller, examined a diagnostically heterogeneous group that probably included patients with multi-infarct dementia—patients particularly prone to depression (14). Thus, early reports were of studies that either had mixed samples of demented patients or did not diagnose major depression.

All of the patients we studied met current diagnostic criteria for both major depression and Alzheimer's disease. We made diagnoses of major depression rather than describing depressive symptoms because genetic, neurophysiologic, and therapeutic data indicate the importance of this distinction (18).

We used the modified PSE to detect cases of depression because of its demonstrated reliability and validity for other psychiatric patients. With it, we were able to achieve a high level of interrater agreement on diagnoses of major depression and were able to identify a subgroup of Alzheimer's disease patients who were more likely to have past psychiatric histories. The advantage of the modified PSE is that it combines the direct examination of patients with information from informants to arrive at the "best truth" regarding symptoms. This is useful for clinical studies of psychopathology in Alzheimer's disease, since demented patients may be unable to report symptoms because of

their cognitive impairment (18). Thus, the modified PSE served as a tool to structure and combine the examination of patients and families in this study.

The diagnosis of major depression in these cognitively impaired patients raises the question whether they suffered from pseudodementia and not Alzheimer's disease at all. However, all of the patients met the NINCDS criteria for Alzheimer's disease when they were initially examined. The subsequent course of their illness has been progressive, thus increasing our confidence in the diagnosis of Alzheimer's disease and making pseudodementia less likely.

We found that major depression in these patients is associated with greater impairments in cognition and in capacity for self-care. Finding greater cognitive impairment in depressed patients is not unexpected, as depression may worsen already impaired cognition. However, an alternative explanation is that the depressed patients were receiving more psychotropic medications than the nondepressed patients. These medications often have anticholinergic activity, which may exacerbate central cholinergic deficits already present in Alzheimer's disease and further impair cognition.

We also found that the depressed patients were more disabled in activities of daily living than the nondepressed patients. Depression may have rendered these patients apathetic or uninterested in their self-care, or anticholinergic medications may have contributed to their disability (19). The design of the study did not permit us to clarify the relationships among depression, use of medication, impaired cognition, and capacity for self-care or to determine whether some degree of disability in these areas is reversible. However, two recent placebo-controlled, double-blind clinical trials of antidepressants (20, 21) suggested that these drugs improve the mood and functioning of some depressed demented patients but are less likely to improve or worsen cognition.

The 17% prevalence rate of depression in our sample was higher than expected for this age group and higher than the rate reported in medically ill elderly outpatients (22, 23). How can we understand this rate of depression in Alzheimer's disease? Almost one-third of the depressed patients had had previous episodes of psychiatric illness, usually depression. This agrees with Kral's (24) and Agbayewa's (25) reports that patients with Alzheimer's disease are more likely than nondemented patients to have had psychiatric illnesses earlier in life. Since these past episodes occurred before the onset of dementia, some patients may have been predisposed to depression because of preexisting psychological or genetic vulnerability. Alternatively, our group has reported (26) that depression in Alzheimer's disease may be associated with fewer noradrenergic neurons in the locus ceruleus, suggesting that some individuals have a distinct neuropathology that may predispose them to depression.

Which cases of depression in Alzheimer's disease are due to an understandable reaction, a genetic vulnerability, or a neuropathological process requires further

study. In this study, however, we identified a subgroup of patients with Alzheimer's disease and major depression who were more cognitively impaired and more socially disabled than nondepressed patients. The fact that they were taking a variety of psychotropic medications, including antidepressants, emphasizes the importance of recognizing and finding new ways to treat depression in Alzheimer's disease.

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Role of γ -Aminobutyric Acid in Antipanic Drug Efficacy

Michael F. Breslow, M.D., Martha P. Fankhauser, M.S., Rebecca L. Potter, M.D., Keith E. Meredith, Ph.D., John Misiaszek, M.D., and Deane G. Hope, Jr., M.Ed.

All effective pharmacologic agents used to treat panic disorder augment γ -aminobutyric acid (GABA) transmission. Anxiolytics and antidepressants that block GABA activity are not effective in panic disorder. To test the hypothesis that GABA activity is a component of antipanic drug efficacy, the authors treated 10 medication-free panic disorder subjects with oral baclofen (30 mg/day for 4 weeks) in a double-blind, placebo-controlled crossover trial. Baclofen, a selective GABA agonist, was significantly more effective than placebo in reducing the number of panic attacks and scores on the Hamilton anxiety scale, Zung scale, and Katz-R nervousness subscale. The authors discuss possible mechanisms of antipanic drug efficacy.
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Monoamine oxidase inhibitors (MAOIs) (phenelzine) (1, 2), tricyclic antidepressants (imipramine [1], desipramine [3]), and benzodiazepines (al-

prazolam [4], clonazepam [5], diazepam [6]) are the most effective pharmacologic treatments for panic disorder. Although the mechanism of action responsible for the antipanic efficacy of these agents is unknown, all antidepressant and antianxiety drugs that produce antipanic effects also augment γ -aminobutyric acid (GABA) transmission (7-15). GABA, the major inhibitory neurotransmitter in the central nervous system (CNS), is involved with 30%-50% of all neurons (16). GABA receptor activation increases permeability of the chloride channel in postsynaptic membranes, thus inhibiting membrane depolarization (16, 17).

Acute treatment with tricyclics and MAOIs increases brain GABA activity in rats, possibly by inhibiting reuptake and degradation (7, 8). With chronic use, the antipanic antidepressants phenelzine, imipramine, and desipramine up-regulate GABA receptors (9-11). In contrast, the antidepressant bupropion has no effect on GABA receptors (12) and is not effective in panic disorder (13).

The interaction of alprazolam, clonazepam, and diazepam with the benzodiazepine receptor increases the number of functional GABA receptors and their affinity for GABA (14). In contrast, the antianxiety agent buspirone has no effect on GABA receptors (15) and lacks antipanic efficacy. Sheehan, in an unpublished study, treated 52 panic disorder subjects in an 8-week double-blind parallel trial of imipramine, buspirone (mean dose, 57.5 mg/day), and placebo. Imipramine was superior to buspirone and placebo on measures of antipanic efficacy. Buspirone was no better than placebo for treating panic symptoms.

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Because all antidepressant and antianxiety drugs that produce antipanic effects also augment GABA transmission and because antidepressant and antianxiety agents that lack GABA activity are not efficacious in panic disorder, we hypothesized that enhancement of GABA transmission is the mechanism of action that results in antipanic efficacy. To test this hypothesis, we treated nine drug-free panic disorder subjects with the selective GABA agonist baclofen (18).

METHOD

We sought individuals 18–65 years old who had a minimum 6-month history of illness consistent with *DSM-III* criteria for panic disorder, had had at least one panic attack weekly for the previous 4 weeks, and had a minimum Hamilton Rating Scale for Anxiety (19) score of 18. Exclusion criteria for this study were 1) current use of medication, 2) history of other major psychiatric disorders (major affective disorder, schizophrenia, substance abuse), and history of illness that might cause anxiety symptoms (e.g., endocrine disorders, cardiovascular disease, including mitral valve prolapse, respiratory disease, and diabetes mellitus). We screened 307 individuals by telephone who responded to newspaper advertisements soliciting subjects, and most were excluded because they were using benzodiazepines or antidepressants.

Applicants who seemed to meet the inclusion criteria ($N=27$) were scheduled for formal psychiatric and medical evaluation. The procedure was explained to them and informed consent was obtained. They were evaluated by psychiatric residents blind to the nature and purpose of the study. Of the 27, 18 were diagnosed as having *DSM-III* panic disorder, and 16 of the 18 underwent medical screening, which included a medical history, physical examination, and laboratory testing (serum electrolytes, liver function enzymes, thyroid function tests, CBC, and urinalysis).

Thirteen subjects were found to be healthy and were offered treatment. They were then interviewed by the investigators to assess the severity and frequency of their panic symptoms. Because of possible clinically significant effects on panic symptoms (20), they were instructed not to consume caffeine, chocolate, ethanol, monosodium glutamate, and nicotine after being counseled about common foods and drinks containing these substances.

After a 2-week drug-free period, the Hamilton anxiety scale, Beck Depression Inventory (21), SCL-90 (22), Zung Anxiety Scale (23), and Katz Social Adjustment Scale—Relatives Form (Katz-R) (24) were completed to obtain baseline scores, and four subjects were dropped from the study because their Hamilton anxiety scale scores were below 18 or they did not have at least one panic attack each week. The remaining nine subjects (five women and four men) were randomly assigned to receive either baclofen or placebo in a double-blind manner. The mean ages of the female and

male subjects were 40 years (range, 31–52 years) and 27.8 years (range, 18–43 years), respectively.

The study duration was 14 weeks, which included an initial treatment course of 6 weeks (1 week during which the dose was gradually increased, 4 weeks of treatment three times a day with either baclofen, 10 mg p.o., or identically appearing placebo, and a 1-week tapering phase). After a 2-week drug-free period, subjects were crossed over to the alternate agent for an identical treatment course.

The subjects were required to record each panic attack, listing its duration and time, and complete a side effects rating scale daily. The SCL-90, Beck inventory, Zung scale, Hamilton anxiety scale, and Katz-R scale were repeated at weeks 5 and 13 to assess the effect of 4 weeks of therapy with baclofen or placebo.

An analysis of variance (ANOVA) with repeated measures was used to examine the effect of receiving baclofen on all treatment measures. There was one between-group variable, treatment order, with two levels, baclofen followed by placebo and placebo followed by baclofen. There was one repeated measures variable, trials, with three levels, baseline, postplacebo, and postbaclofen. The design provided three F ratios that allowed for tests of effects of treatment order, trials, and the two-way interaction. All F ratios were tested for significance at $p<0.05$.

RESULTS

The interaction between treatment order and trials was not significant, indicating that order of exposure to baclofen or placebo did not contribute to the results. No treatment order F values were significant, an expected finding because of random assignment. To further verify the effectiveness of randomization, the baseline means of the two treatment order groups were compared by using the Newman-Keuls post hoc test, and no significant differences were found.

The trials effects were directly interpreted, given the nonsignificant interaction and treatment order effects. Significant trials effects ($p<0.05$) were found for number of panic attacks, Hamilton anxiety scale scores, Zung scale scores, SCL-90 anxiety, interpersonal sensitivity, and depression subscale scores, Katz-R nervousness subscale scores, and Beck depression scores. For those variables demonstrating significant trials effects, pairwise comparisons were conducted for each of the three combinations of trial means (baseline-postbaclofen, baseline-postplacebo, and postbaclofen-postplacebo) by using the post hoc Newman-Keuls test. As shown in table 1, number of panic attacks, Hamilton anxiety scale scores, Zung scale scores, and Katz-R nervousness subscale scores demonstrated significant differences for the baseline-postbaclofen and the postbaclofen-postplacebo comparisons. These results suggest that significant change was related to treatment with baclofen. Significant differences were also found in the baseline-postbaclofen and baseline-

TABLE 1. Results of Crossover Study of Baclofen and Placebo in Nine Patients With Panic Disorder

Variable	Baseline		After 4 Weeks of Treatment				Significant Trials Effect (p<0.05)		Post Hoc Comparison (Newman-Keuls)		
			Placebo		Baclofen		F	df	Baseline-Postbaclofen	Baseline-Postplacebo	Postbaclofen-Postplacebo
	Mean	SD	Mean	SD	Mean	SD					
Panic attacks per week	7.9	7.3	6.8	9.2	2.2	2.1	4.72	2, 14	p<0.05	n.s.	p<0.05
Hamilton anxiety scale score	25.2	4.2	22.3	10.1	16.1	7.6	6.69	2, 14	p<0.05	n.s.	p<0.05
Zung Anxiety Scale score	56.2	10.8	52.3	14.6	45.0	10.0	5.61	2, 12	p<0.05	n.s.	p<0.05
SCL-90 subscale											
Anxiety score	17.2	8.1	12.3	11.1	8.0	7.2	8.95	2, 14	p<0.05	p<0.05	n.s.
Interpersonal sensitivity score	10.3	7.5	5.0	6.1	3.0	4.6	9.52	2, 14	p<0.05	p<0.05	n.s.
Depression score	19.4	13.9	12.3	13.1	8.3	11.5	9.46	2, 14	p<0.05	p<0.05	n.s.
Beck Depression Inventory score	16.9	10.3	11.8	15.2	8.4	13.5	4.29	2, 14	p<0.05	n.s.	n.s.
Katz-R nervousness subscale score	10.3	2.6	8.9	3.9	6.9	1.5	7.81	2, 10	p<0.05	n.s.	p<0.05

Postplacebo post hoc comparisons for the SCL-90 anxiety, interpersonal sensitivity, and depression subscale scores (table 1). The fact that change in these variables existed in both the baclofen and placebo treatment conditions demonstrates both a drug and placebo effect. A trend toward greater change resulting from baclofen rather than placebo was observed in all of these variables but was not strong enough to result in a significant difference in the postbaclofen-postplacebo comparison. Post hoc tests conducted with the Beck scores resulted in a significant difference in the baseline-postbaclofen comparison, but there was no significant postbaclofen-postplacebo difference.

Of the 11 side effects rated daily, only drowsiness and confusion were reported more frequently with baclofen than with placebo. In all cases, these effects were transient and mild. No subjects needed to discontinue treatment or have their doses reduced.

DISCUSSION

In this pilot study, baclofen was more effective than placebo in reducing the number of panic attacks and symptoms of anxiety (assessed with the Hamilton anxiety scale and the Zung Anxiety Scale) in nine patients with panic disorder. These improvements were corroborated by a significant difference in postbaclofen-postplacebo scores on the Katz-R nervousness subscale and a nonsignificant trend on the SCL-90 anxiety subscale. Significant improvement on four of five measures of anxiety and no significant improvement on nonanxiety scales suggest a powerful, specific effect for baclofen in treating panic anxiety.

Although we excluded individuals who met DSM-III criteria for major affective disorder, some subjects also had depressive symptoms. Controlled clinical trials (25) have shown that selective GABA agonists have antidepressant effects. In our study, baclofen was no more effective than placebo in treating depressive symptoms. Thus, its effect on anxiety seems to be independent of any antidepressant activity. Its failure to achieve significant results over placebo on the SCL-90 anxiety subscale may be related to the low number of

items on this subscale and the sizeable effect of placebo on this assessment.

Baclofen is a selective agonist for a subtype of GABA receptors, GABA-B receptors. These receptors are functionally associated with β -adrenergic receptors and affect the coupling of adenylate cyclase with the β -adrenoceptor (26). Activation of GABA-B receptors results in increased cAMP production for any given stimulation of the β -adrenergic receptors (27). At the dose of baclofen used in our study, down-regulation of β -adrenergic receptors has not been reported in animal studies (26–28); in addition, earlier work (6) showed a lack of efficacy for the β blocker propranolol in panic disorder. Therefore, the antipanic efficacy we observed does not appear to be secondary to β receptor regulation. Whether the efficacy of baclofen is related to its effect on β -adrenergic receptor-adenylate cyclase coupling or to another GABA effect, such as an interaction with serotonin (28) or other neurotransmitter systems, requires further study.

On the basis of our results, baclofen appears to be an effective agent for the treatment of panic disorder. The fact that our subjects reported few side effects may have contributed to the zero dropout rate. This study was limited by the small sample size (N=9). If larger studies confirm our preliminary data, baclofen's efficacy in treating panic disorder will further support the hypothesis that enhancement of GABA transmission may be a key pharmacologic component in antipanic drug efficacy.

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Maintenance of an Insanity Defense Under Montana's "Abolition" of the Insanity Defense

Henry J. Steadman, Ph.D., Lisa A. Callahan, Ph.D.,
Pamela Clark Robbins, B.A., and Joseph P. Morrissey, Ph.D.

In 1979, Montana's insanity defense was replaced with the more restrictive mens rea defense, a change that has been described as an example of "abolition" of the insanity defense. The authors identified cases in which mental health was an issue in seven Montana counties for 3 years before and 3 years after the 1979 reform. They found that acquittals based on the insanity plea markedly declined, but that dismissals based on incompetence to stand trial increased substantially following the reform. They conclude that dismissal based on incompetence to stand trial became a substitute for acquittal based on the insanity plea under mens rea.

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Before John Hinckley's insanity acquittal in 1982, the two major revisions in insanity defense proceedings in the United States in the previous decade had been the introduction in 1975 of the guilty but mentally ill verdict in Michigan and the abolition of the insanity defense in Montana in 1979 and in Idaho in 1982. The change to a guilty but mentally ill verdict has been highly visible due to several research reports on the Michigan experience (1-3) as well as its adoption in seven other states. The abolition of an insanity defense in Montana and Idaho, in contrast, has generally been accepted at face value. To our knowledge, no follow-up research in either state has been reported. The focus in this paper is on the Montana experience.

The intent of this paper is twofold. First, we argue that the introduction of a *mens rea* defense is not an abolition of the insanity defense but, rather, a limited insanity defense. Second, we maintain that the development of a *mens rea* defense shifts the processing of

mentally ill defendants from judicial decision to the pretrial negotiation between defense and prosecution attorneys. Our data from Montana support both assertions. Montana's affirmative defense of not guilty by reason of insanity was eliminated in a 1979 reform. Although this special, separate defense was abolished, the *mens rea* section of the law was left intact. Neither the insanity plea nor the insanity verdict was changed when Montana adopted the *mens rea* insanity defense. The plea is still an insanity plea. The verdict is still "not guilty due to mental disease or defect." The procedures and requirements for the introduction of testimony about mental disease or defect were not changed. What was changed by eliminating the affirmative defense is that now insanity is treated as part of the criminal trial. Further, Montana's *mens rea* defense requires that the question of insanity go to a jury. Under the old law, a judge or jury could determine sanity.

It is common for writers on the insanity defense to state simply that Montana and Idaho have abolished it. For example, in 1982, Arenella (4) observed, "Montana and Idaho have already abolished the defense" (p. 272). In the same year, Lauter (5) said, "In 1979, Montana became the first state to effectively eliminate the separate defense of insanity" (p. 12). In 1985, Geis and Meier (6) also noted that Montana had "abolished the insanity plea" (p. 73).

These commentators reflected the widely held belief that Montana no longer has an insanity defense, and that there have been no insanity acquittals since its abolition in 1979. In fact, neither belief is accurate. A closer look at the Montana law shows that there is still a *mens rea* rule of law that relies on traditional psychiatric testimony but allows for only a limited insanity defense (7). Further, as will be reported later in this paper, when pre- and postreform data on the actual operation of the Montana system are examined, it is apparent that there are still many insanity pleas, that there continues to be a small number of insanity acquittals, and that there is still a system of detention that retains persons indefinitely in a maximum security ward at the state mental hospital under criminal mental health detentions just as there was before 1979.

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MONTANA'S REVISION OF THE INSANITY DEFENSE

In contrast to most insanity defense reforms, Montana's was not precipitated by a notorious case. Rather, a then-freshman legislator, Michael Keedy, simply attacked the old law, which was a modified American Law Institute standard that found a defendant not guilty by reason of insanity if, as a result of mental disease or defect, he or she was "unable to appreciate the criminality of his conduct or conform his conduct to requirements of law" (8).

In an interview with our project staff conducted in Kalispell, Mont., on September 13, 1985, Keedy said that his reasons for sponsoring a change in the insanity defense were both legal and social. He said that, legally, a separate insanity defense was not necessary because the requisite state of mind is an essential element of the state's case and, socially, he was motivated to change the law because of the public's negative perception of the insanity defense. He added that psychiatric testimony deflects attention from the real issues of culpability.

The new law in 1979 did not, however, completely remove the issue of mental state at the time of the offense. The *mens rea* section of Montana's law states that "when the defendant is found not guilty . . . due to a mental disease or defect he could not have a particular state of mind that is an essential element of the offense charged" (9). It still requires that the defendant have the requisite mental state to purposely or knowingly form intent. In other words, there remains a requisite *mens rea* test under which psychiatric testimony on mental state at the time of the offense could be introduced.

Given this feature of the law, which retains an option, albeit much more restrictive, for psychiatric exculpation, it becomes an empirical question as to whether Montana's *de jure* abolition of a special insanity defense has, in fact, done away with insanity cases in the courts and mental hospitals. Further, to adequately examine the impact of the implemented reforms, both acquittal and plea data are required. Without plea data, an absence of acquittals after 1979 could mean simply that judicial and jury decision making had changed rather than imply that the insanity plea had been abolished. The defense might have been heavily used but with minimal success.

METHOD

The data reported here are drawn from an eight-state, 5-year study that we are currently conducting. We are examining the impact of various types of insanity defense reforms on the volume and characteristics of persons pleading insanity and acquitted by reason of insanity. We are focusing on changes in the insanity test itself. The study reforms include changes in postdisposition processing, such as shifting the court responsible for release decisions; changes in the burden

of proof in release hearings; and changes in which both pre- and postdisposition processes were altered, such as the guilty but mentally ill judgment. Five of the states involved in the study (Montana, Ohio, Georgia, California, and New York) were chosen for the type of insanity defense changes they made, and three (New Jersey, Washington, and Wisconsin) were selected for comparison because they made no statutory changes during the study period. Data collection began in 1985; Montana is the first state for which data are available.

Our design involves obtaining insanity plea and acquittal data for 3 years before and 3 years after the reform of interest or, in the case of the comparison states, for 1982, the year of John Hinckley's acquittal. Acquittal data were obtained from manual and automated state information systems. These sources provide key data on all acquittals across each state. Plea data are much more difficult to acquire because they are maintained only at the county level. To obtain data in eight states in a reasonably cost-effective manner we selected counties that produced two-thirds of a state's not guilty by reason of insanity acquittals. On the assumption that the number of acquittals and the number of pleas are highly correlated, this criterion would yield a sample that included approximately two-thirds of a state's pleas. In Montana this meant that we studied seven of the state's 56 counties.

In these seven counties, our field staff reviewed court docket books for the years 1976 through 1985 to identify every case in which an insanity plea was entered or in which there was a court order for a psychiatric examination for mental disease or defect. The file for each of the cases identified was then pulled in the court clerk's office, and a wide range of demographic, criminal history, current charges, and court processing items were abstracted onto our standard form. Institutionalization data on all pleas and all acquittals were obtained from the Montana Department of Institutions. After the data collection forms were completed for Montana, they were forwarded to Albany, N.Y., where they were reviewed, cleaned, keyed, and analyzed.

In this paper we analyze only the three years before and three years after the reform. The additional data will be used for subsequent analyses. The thrust of this analysis was to see whether insanity pleas and acquittals were abolished by the statutory changes and, if not, how the new system was functioning. It is important to note that in the analyses that follow, acquittal data are statewide, but plea data are from seven counties.

RESULTS

As the question of the impact of the Montana abolition of the insanity defense would usually be framed, acquittal data are key. In the 3 years before the reform (July 1976–June 1979), there were 22, 21, and 18 insanity acquittals, respectively, statewide. Following the

TABLE 1. Outcome of Insanity Pleas in Seven Montana Counties Before and After 1979 Reform^a

Outcome	Before (N=69)		After (N=80)	
	N	%	N	%
Guilty	27	39.1	44	55.0
Not guilty	2	2.9	2	2.5
Not guilty by reason of insanity	22	31.9	2	2.5
Guilty but mentally ill	1	1.4	0	0.0
Charges dismissed	14	20.3	26	32.5
Case deferred	2	2.9	5	6.3
Case pending	1	1.4	1	1.3

^aTwo other pleas were entered, but no information was available as to the verdict.

reform (July 1979–June 1982), there were two, three, and none, respectively. It is important again to emphasize that statutorily a *mens rea* defense does not eliminate insanity acquittals. The process by which a defendant is acquitted is what changes. Clearly, since there were five insanity acquittals after the reform, the insanity plea was not abolished. Of further note is the fact that all five of these cases were initiated after the reform; they were not carryovers from the period before the reform.

Further evidence of the insanity plea's continuation is apparent from the plea data from the seven counties studied. In the 3 years before the reform, there were 71 insanity pleas, and in the 3 years after the reform there were 80. To see what happened to these pleas both before and after the reform, we pursued the data presented in table 1. Before the reform, 32% of insanity pleas were successful, but only 3% were successful after the reform. The two other major shifts were the percents of persons found guilty, which increased from 29% to 55%, and the number of cases dismissed, which increased from 20% to 33%.

To understand what these data really mean, we took suggestion from one of the senior staff members at Montana State Hospital. She told us that if we wanted to understand what was going on under the new law, we should look at the people being found incompetent to stand trial because that was how those who would have had insanity acquittals were now being handled.

On the basis of that suggestion, we analyzed the data presented in table 2 for all defendants found incompetent to stand trial in the 3 years before and the 3 years after the 1979 reform. Before the reform, most persons found incompetent to stand trial were subsequently found not guilty by reason of insanity (63.6%), and the cases of almost one-fourth of those found incompetent to stand trial ultimately were dismissed. After the "abolition" of the insanity defense, only 5% of those found incompetent to stand trial were found not guilty by reason of insanity, but the cases of 75% were dismissed. There are two typical scenarios for persons initially found incompetent to stand trial. In one the defendant is restored to competency and returned to court and tried, which some-

TABLE 2. Final Verdict of Incompetent to Stand Trial Cases in Seven Counties Before and After Montana's 1979 Reform

Final Verdict	Before (N=33)		After (N=40)	
	N	%	N	%
Guilty	2	6.1	2	5.0
Not guilty	0	0.0	0	0.0
Not guilty by reason of insanity	21	63.6	2	5.0
Guilty but mentally ill	0	0.0	1	2.5
Charges dismissed	8	24.2	30	75.0
Case deferred	2	6.1	4	10.0
Case pending	0	0.0	1	2.5

times leads to an insanity acquittal. In the other, the defendant is not restored to competence within the statutorily prescribed time and the charges are dismissed. The first group of defendants are subject to commitment under criminal procedures; the latter are subject to civil commitment procedures.

What is important about these dismissals is that two-thirds of the persons whose charges were dismissed were committed indefinitely under the civil mental health code to Montana State Hospital (data not shown) and that they were often treated there on the same units as were patients found not guilty by reason of insanity both before and after the reform. Clearly, after the reform substantially more defendants pleading insanity were convicted. Presumably that had been a main goal of the reform. At the same time, more persons pleading insanity had their charges dismissed. However, these persons were not released but were committed to the same units, in the same facility, for indefinite periods of time, just as had been those who were found not guilty by reason of insanity under the old American Law Institute insanity plea. Moreover, no longer were persons who were found incompetent to stand trial subsequently found not guilty by reason of insanity. Instead, they, too, had their charges dismissed and often were committed indefinitely to the state mental hospital's security unit.

Thus, although for most persons a special defense of insanity was abolished in Montana by the 1979 reform, the goal of long-term retention in a maximum security state hospital of mentally ill persons who violate criminal laws was retained in practice through the determination of incompetence to stand trial and the subsequent dismissal of charges and indefinite civil commitment. The insanity statutes were reformed, but the detention system was not. Real reform of the system would require a complete, integrated overhaul of a wide range of statutes and regulations that affect or are affected by the insanity defense. Such reform, a major undertaking, would have rippling effects throughout many systems that could be problematic due to many unanticipated repercussions. The effect of even a single statutory revision—that of the *mens rea* statute on incompetency determinations—is demonstrated here.

DISCUSSION

These data demonstrate that neither in statute nor in practice has the insanity defense been abolished in Montana. Five insanity acquittals in the first 3 years after reform represent a radical reduction in formal acquittals, but radical reduction is not abolition. These data support the idea that the *mens rea* defense is still an insanity defense.

Our data suggest that under Montana's *mens rea* law, mentally ill defendants are being eliminated from criminal justice processing at an earlier stage. It could be argued that incompetency is more reliably determinable than criminal insanity, and that moving the consideration of mental illness to the pretrial stage through use of the incompetent to stand trial finding, dismissal of charges, and civil commitment places the consideration of mental illness as a factor at a more appropriate time in the criminal justice process.

Another way to view these data is to conclude that the mental health system has simply been manipulated to produce a functional equivalent for formal insanity acquittals. By means of an incompetent to stand trial finding, it appears that persons who would have been found not guilty by reason of insanity under the old law have had their charges dismissed and been committed indefinitely to the same facility to which those acquitted by reason of insanity had been retained. This suggests that "abolition" of the insanity defense may occur only in those jurisdictions where state regulations and facilities allow the maintenance of old ways under new statutes.

Regardless of which point of view one may hold, what is most important to conclude from these data is that statutory reform cannot be accepted at face value in insanity defense issues. Data on subsequent practice must be obtained. Our results are analogous to the findings of Geller and Lister (10) that when the Massachusetts mental health code tightened involuntary civil commitment standards, evaluations for competency to stand trial were used as an alternative mechanism to detain persons in civil state hospitals.

Our results also point out the need to obtain plea data to fully understand insanity defense issues. To have had only acquittal data in Montana never would have illuminated the relationships between incompetent to stand trial findings and the subsequent disposition of these cases.

County-level plea data are much more difficult and costly to gather, but if we are to adequately understand the actual operations of the insanity defense and its applications for psychiatry and the criminal justice system, future work must more regularly rely on plea data along with acquittal data provided by state information systems.

The complexities of insanity defense reform will not be probed effectively until more research is undertaken that focuses on the plea of insanity and on the comprehensive follow-up of the actual effects of insanity defense reform. As Brooks (11) noted, "Two modestly populated states, Idaho and Montana, have enacted *mens rea* statutes. Their future experience should be carefully evaluated. If a more heavily populated state were to adopt the *mens rea* approach, there would be an even better opportunity to evaluate its validity. But unless that happens, we will have no way of knowing whether the *mens rea* is superior to other approaches or not" (pp. 135, 136). Following his suggestion here, we have demonstrated an operating system far different from that generally depicted in the professional literature, one with quite different implications for the field of psychiatry.

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Psychometric Assessment of First-Degree Relatives of 62 Autistic Probands in Utah

B.J. Freeman, Ph.D., Edward R. Ritvo, M.D., Anne Mason-Brothers,
Carmen Pingree, M.S., Alice Yokota, William R. Jenson, Ph.D.,
William M. McMahon, M.D., P. Brent Petersen, M.D., Amy Mo, and Phillip Schroth

The Wechsler Intelligence Scales, Wide Range Achievement Test, and the Shipley-Hartford Test were administered to 122 parents and 153 siblings of 62 autistic probands in Utah. Scores were distributed as expected within the published normative ranges for each scale. Parents' scores correlated with those of their nonautistic children, but neither parents' nor siblings' scores correlated with the IQ level of the autistic probands. These results do not confirm prior reports from England and the United States of a high rate of cognitive and learning problems in the siblings of autistic individuals, nor the aggregation of such problems in the siblings of probands with high or low levels of cognitive function.

(Am J Psychiatry 1989; 146:361-364)

Several studies have reported an unusually high prevalence of cognitive dysfunction, learning problems, and mental retardation among siblings of autistic probands (1-6). These disorders are manifested by poor performance on standardized psychometric tests, histories of delayed language, and clinical evidence of specific cognitive defects. Two of the studies also noted aggregation of these disorders in siblings of families with high-IQ (1) and low-IQ (5) autistic probands.

Bartak et al. (1) and Folstein and Rutter (2) suggested that a high prevalence of learning problems could indicate that a language or cognitive deficit is inherited and, when combined with an environmental perinatal insult, could produce autism. On the other hand, Baird and August (5) reported "a significant clustering of autism and nonspecific intellectual retar-

dation in the siblings of severely retarded autistic probands that was not present in the siblings of our higher functioning autistic sample"; thus, "the transmittal factor may pertain to a more general cognitive impairment or mental retardation. Conceivably it is this low functioning subgroup [of autistic probands] that has shown a familial genetic loading."

In a related study, Minton et al. (4) observed that 7% of the siblings of probands had Wechsler Full-Scale IQs of 69 or below, compared to 2% in the normative sample. They also noted that many of these siblings had lower verbal scores than performance scores, a common finding in autistic patients.

These studies were limited by their methods of ascertainment, small sample sizes, and failure to directly test parents and did not compare the results of their standardized tests to published normative data. In addition, since *DSM-III* criteria were not available for the pre-1980 studies (1, 2), the issue of patient comparability exists and limits interpretation of their results. However, taken together, these studies suggest that a more comprehensive study of both parents and nonautistic siblings could shed light on possible genetic factors that contribute to the etiology of a subgroup of autistic patients.

The present study was designed to assess both parents and nonautistic siblings on standardized psychometric scales and to correlate these data with information on the cognitive levels of their probands. Specifically, we wished to test the following hypotheses based on prior studies: 1) Significantly more parents or siblings of autistic probands score below one standard deviation from published normative means on psychometric tests, and 2) the parents and siblings with the low scores aggregate in families of probands with either high or low IQs.

Equally tenable alternative hypotheses that we formulated and wished to test simultaneously were as follows: 1) The distribution of parents' and siblings' scores fall within the published normative ranges of the scales, 2) parents' scores correlate with those of their nonautistic children, and 3) parents and siblings with low scores do not aggregate in families of probands with either high or low IQs.

Received Feb. 11, 1988; revision received June 24, 1988; accepted Sept. 9, 1988. From the Division of Mental Retardation and Child Psychiatry, UCLA School of Medicine, Los Angeles, and the University of Utah, Salt Lake City. Address reprint requests to Dr. Freeman, Neuropsychiatric Institute and Hospital, 760 Westwood Plaza, Los Angeles, CA 90024.

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METHOD

We have recently conducted an epidemiologic survey throughout the state of Utah. A four-level ascertainment system was used. A total of 489 possibly autistic individuals born during the period 1960–1984 and living in Utah during the survey (1984–1988) were ascertained, and 241 were diagnosed as autistic. They came from 187 single-incidence families and 20 multiple-incidence families. Genetic research has shown no excess of inbreeding or consanguinity in Utah, and the gene pool is fully representative of North America and the European Caucasian population (7, 8). Thus, all the families studied were drawn from a well-defined and epidemiologically valid population.

We selected families of the first 62 autistic probands enrolled in the UCLA—University of Utah Autism Research Project in which both parents were available for testing and in which there was one or more nonautistic siblings 4 years or older. Probands were diagnosed according to a research protocol that included a 500-item developmental inventory (9, 10) and pregnancy, delivery, medical, psychological, and educational records; a retrospective diagnosis of autism by two blind reviewers (E.R.R. and B.J.F.) based on reports of development before 30 months of age; and a blind current diagnostic family interview and mental status examination in Utah (by W.R.J., P.B.P., and W.M.M.). Each proband clearly met the *DSM-III* and the Autism Society of America's criteria for the syndrome of autism (11). All tests were administered during home visits (by B.J.F. and A.Y.). Confidentiality was assured, and appropriate human subject protection committee approvals were obtained when necessary.

Siblings who had not completed high school were given age-appropriate Wechsler scales—the Wechsler Pre-school and Primary Scale of Intelligence for ages 4–6, the WISC-R for ages 6–16½, and the WAIS for ages 16½ and older (12–14). Parents and siblings who had completed high school were given the Shipley-Hartford Test (15). The Wide Range Achievement Test (WRAT-R) was given to all parents and siblings over 5 years of age (16). A questionnaire was administered to parents to obtain information on the siblings concerning onset of language and current work or school placement and performance. Seven probands were given IQ tests, and the remainder of the scores were abstracted from prior records.

The statistical procedures used included chi-square goodness of fit, *z* test for difference from population mean, *t* test for differences between sample means, and Pearson correlation coefficients (17). All statistical computations were accomplished with the Statistical Analysis System (18).

RESULTS

One hundred twenty-two of 124 parents (98%) were tested (one mother was in a psychiatric hospital

TABLE 1. Psychometric Test Scores of Parents of Autistic Probands

Variable	Mothers ^a (N=60)		Fathers ^a (N=62)		Normative Data (%)
	N	%	N	%	
Shipley-Hartford Test ^b					
Conceptual quotient					
Score >85	53	88	46	75	84
Score 70–85	7	12	14	23	14
Score <70	0	0	2	2	2
WRAT-R ^b					
Reading					
Score >85	50	86	54	88	84
Score 70–85	7	12	4	7	14
Score <70	1	2	3	5	2
Spelling					
Score >85	53	88	47	78	84
Score 70–85	5	8	7	12	14
Score <70	2	3	6	10	2
Arithmetic					
Score >85	46	77	54	88	84
Score 70–85	13	22	4	7	14
Score <70	1	2	3	5	2

^aThe mean±SD ages of the mothers and fathers were 40±6 and 43±7 years, respectively.

^bThe mean±SD scores for the mothers, fathers, and normative data were 102±11, 94±16, and 100±15 on the Shipley-Hartford conceptual quotient (significant difference between fathers and normative data; *t*=3.09, *df*=61, *p*<0.01); 103±13, 102±16, and 100±15 on the reading scale; 104±14, 97±18, and 100±15 on the spelling scale (significant difference between mothers and fathers; *t*=2.12, *df*=120, *p*<0.05); and 97±13, 101±14, and 100±15 on the arithmetic scale.

with the diagnosis of schizophrenia, and one mother was uncooperative). As shown in table 1, the means and standard deviations for the conceptual quotient on the Shipley-Hartford Test and the scores on the WRAT-R closely approximated the normative published values (13, 14). Fathers' and mothers' mean scores showed only slight differences. The fathers' mean conceptual quotient was significantly different from normal (*p*<0.01). The mothers had a higher mean score than the fathers for spelling (*p*<0.05).

A Hollingshead two-factor social class score (19) was computed for each family. Twenty-five percent of the families were in social class I, 11% in class II, 27% in class III, 31% in class IV, and 5% in class V. The observed and expected distributions were not statistically significant (36% and 41% for classes I and II, 27% and 23% for class III, and 36% and 36% for classes IV and V; $\chi^2=1.56$, *df*=2, *n.s.*).

One hundred fifty-three of 156 siblings (98%) were available for testing (one adult was uncooperative, and two adults had moved from Utah during the study). There were 78 male and 75 female siblings. Of the male siblings, 16 were adults and 62 were children; of the females, 14 were adults and 61 were children. The mean±SD ages of adult female and male siblings were 26±5 and 22±3 years, respectively; for the child female and male siblings they were 11±4 years.

The means and standard deviations of the scores of the adult siblings on the Shipley-Hartford Test and the

WRAT-R, and of the child siblings on the age-appropriate Wechsler scales (10–12), did not differ significantly from the published normative values for these scales. The mean IQs on the Wechsler scale for the child siblings were higher than the published normative values, before correction for social class. However, they were almost identical to the published normative values when they were corrected for social class (full-scale corrected normative means IQ for boys=115 and for girls=110) (20).

On the Wechsler scales none of the girls and 1.6% of the boys had full-scale IQs of 70 or below, which was very close to the published normative value of 2% (10–12). In addition, 17 of the child siblings had performance IQs that were significantly greater (15-point difference) than their verbal IQs, and 19 had verbal IQs that were greater than their performance IQs.

The means and distributions of scores on the WRAT-R were almost identical to the published normative values for each scale (14). Adult male siblings had a tendency to score lower than expected on the mathematics scale (31.3% had scores between 70 and 75, but none scored below 70), but the difference was not statistically significant. This difference is probably an artifact due to the small sample size, since it was not present in the larger sample of child siblings.

The distribution of IQs by social class for all of the siblings was not skewed (classes I and II, mean IQ=111.9; class III, mean IQ=119.56; classes IV and V, mean IQ=110.4).

There were positive correlations between the means of the mothers' and fathers' IQs and the mean of the child siblings' full-scale Wechsler IQs ($r=0.43$, $N=23$, $p\leq 0.05$) and between the mean of the parents' and child siblings' scores on the WRAT-R reading ($r=0.21$), spelling ($r=0.19$), and arithmetic ($r=0.27$) scales ($N=118$, $p\leq 0.05$ for all comparisons). While these correlations were statistically significant, they accounted for only a small percentage of the variance and should be viewed as only suggestive.

For the purposes of this study, we defined a "learning problem" as a score of more than one standard deviation below the mean on a cognitive test (Shipley-Hartford Test or Wechsler scale) or a subtest of the WRAT-R. (The published normative expected frequency for this occurring is 16.5%.) Parents with learning problems had significantly more children with learning problems than did parents without learning problems ($\chi^2=6.58$, $df=1$, $p=0.01$). When both parents had a learning problem, 84% ($N=5$ of 6) of their children also did. Since there were only two families in which both parents had learning problems, these findings are only suggestive. When one or both parents had a learning problem, 38% ($N=15$ of 39) of their children also did. When only one parent had a learning problem, 33% ($N=10$ of 33) of their children did. When neither parent had a learning problem, 20% ($N=23$ of 114) of their children did. (This rate is similar to the expected rate of 16.5% from normative data.) One family requires special mention. The father

reported delayed onset of speech. In addition to his proband autistic son, he had seven nonautistic children, of whom five had delayed speech onset. Three of these five also scored below 85 on one or more subtests.

Before this study, four of the 62 families were known to have two autistic children. During the study one of these multiple-incidence families was found to have a third autistic child, and three additional families were identified as having a second autistic child. Thus, seven of the 62 families (11.29%) had multiple incidences of autism (six had two autistic children, and one had three autistic children). Each of the newly identified multiple-incidence cases underwent a complete diagnostic evaluation, as described for the probands.

Among the 69 autistic patients (62 probands and eight autistic siblings) the boys' mean \pm SD full-scale IQ was 67.3, and the girls' was 49.4. The 62 probands were divided into three IQ groups (over 70, 50–70, and 49 and lower). No significant relationships were found between these groups and/or the presence or absence of learning problems in mothers, fathers, mothers and fathers combined, child siblings, and child and adult siblings combined.

DISCUSSION

Our results do not confirm prior reports (1–6) that siblings of autistic probands have a high incidence of cognitive or learning problems and that those who do have low scores aggregate in families of probands with either high or low IQs. Rather, we found that scores on psychometric tests were distributed as expected within published normative ranges. In addition, parents' scores correlated with those of the nonautistic siblings, and those who had low scores did not aggregate in families of probands with either high or low IQs.

While these findings indicate a tendency for scores on psychometric tests to aggregate in families, they do not support the hypothesis that there is a genetically determined inherited continuum of brain pathology which ranges in severity from mild cognitive dysfunction to autism (1–6). Rather, the data revealed no evidence of genetic linkage between cognitive dysfunction, learning problems, mental retardation, and autism.

Our study differed from prior ones in that we evaluated parents, had sufficient subjects to correct for social class distribution, and compared our results to published normative values for the tests used. Further studies are needed on larger numbers of families and to obtain more detailed testing of parents and adult siblings with low scores. Furthermore, since developmental changes could influence the identification of cognitive processing pathology, future studies should attempt to assess changes over time in parents, siblings, and probands.

An important and unexpected finding was the identification of new multiple-incidence families. At the

outset of the study, four of the 62 families (6.5%) were known to have multiple incidences of autism. Four previously undiagnosed cases of autism were identified in three families, resulting in a total of seven families (11.29%) with multiple incidences of this disorder. This finding indicates that future diagnostic studies of siblings in families with one autistic proband may lead to the identification of additional autistic members. Baird and August (5) similarly identified new multiple-incidence families when studying siblings of their probands. Thus, the true prevalence of multiple-incidence families is certainly higher than the 2% (7) generally cited. (We reported, in a preliminary, unpublished analysis of the UCLA-University of Utah survey, a sibling risk estimate of 4.4% (95% confidence limits=2.8% to 6.5%) and a recurrence risk estimate of 9.1% (95% confidence limits=5.85% to 13.29%). This new information supports our previous findings, which indicate that a familial subtype or subtypes of autism may exist in which genetic abnormalities program pathological brain development or functioning, which in turn produces the pathognomonic developmental delays and symptoms of autism (21-23). Within this proposed genetic subtype of autism, one would expect varying degrees of penetrance. The present data suggest that individuals with milder cases would not show unique profiles on cognitive tests.

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Salivary Prostaglandin Concentrations: Possible State Indicators for Major Depression

Seiji Nishino, M.D., Ryuji Ueno, M.D., Ph.D., Kazuhiro Ohishi, M.D., Ph.D.,
Toshiaki Sakai, M.D., Ph.D., and Osamu Hayaishi, M.D., Ph.D.

Salivary prostaglandin concentrations were determined in 42 patients with major depressive disorder, 16 patients with minor depressive disorder, and 39 healthy control subjects. The diagnoses were made according to the Research Diagnostic Criteria. The patients with major depressive disorder had higher salivary prostaglandin concentrations than the control subjects, but the patients with minor depressive disorder did not. Furthermore, the salivary prostaglandin concentrations of the patients with major depressive disorder showed a high correlation with the severity of the depression. These results suggest that high salivary prostaglandin concentrations may be state indicators for major depression.

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Prostaglandins exert a variety of effects in various organs as well as the CNS (1). Prostaglandins D₂, E₂, and F_{2α} (PGD₂, PGE₂, and PGF_{2α}, respectively) are the major prostaglandins in the mammalian CNS (1, 2), and they have a multitude of actions, including effects on behavior, sleep, temperature, food intake, and pain (1, 3-5). These special roles of prostaglandins in the CNS suggest that they may be related to some psychiatric syndromes.

Several research groups have investigated the relationship of prostaglandin levels to depression. Linnoila et al. (6) detected high amounts of PGE₂ in CSF from patients with unipolar depression. Lieb et al. (7) and Calabrese et al. (8) proposed that high amounts of PGE₂ in the plasma might be involved in the pathophysiology of depression. Furthermore, we demon-

strated that the salivary levels of not only PGE₂ but also PGD₂ and PGF_{2α} were higher in patients with major depressive disorder than in healthy control subjects, and we speculated that this is one of the indicators of major depression (9). However, it is not clear whether those prostaglandin abnormalities in the depressed patients represent a state indicator, occurring only during the depressive phase, or a state-independent indicator of vulnerability to depression.

The purpose of this study was to determine whether high levels of salivary prostaglandins represent the state of major depression. Hence, we studied the relationship between salivary prostaglandin concentration and the severity of illness in patients with major depression.

METHOD

All 58 patients were men; 42 were diagnosed as having major depressive disorder, and 16 were diagnosed as having minor depressive disorder. The diagnoses were made according to the Research Diagnostic Criteria (RDC) (10) on the basis of clinical interviews and medical records. Patients with current or past histories of serious somatic illness or drug abuse were not included. As a control, 39 healthy men without histories of psychiatric illness were studied. The mean ± SD ages of the three groups are shown in table 1. All subjects gave informed consent.

The severity of depressive illness was assessed just before the sampling of saliva by one or two research psychiatrists using the 17-item Hamilton Rating Scale for Depression (11). If a subject was rated by two raters, the mean score was used. The interrater reliability coefficient (intraclass R) of the two raters was 0.97. Some of the results obtained from these subjects were reported in our earlier study (9). To obtain patients with various severities of depression, we employed a random sampling of outpatients with depressive symptoms regardless of whether they were new patients or were already being treated. We divided the patients with major depressive disorder into three subgroups according to their total scores on the Hamilton scale: severely depressed (score ≥ 18), moderately depressed (score = 8-17), and slightly depressed (score ≤ 7).

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TABLE 1. Salivary Prostaglandin Levels and Saliva Flow Rates in Male Patients With Major or Minor Depressive Disorder and in Healthy Male Control Subjects

Group	N	Age (years)		Hamilton Depression Score		PGD ₂ ^a			PGE ₂ ^b			PGF _{2α} ^c			Rate of Saliva Flow (ml/min)	
		Mean	SD	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	Mean	SD
Major depressive disorder ^d	42	47.2	10.2	13.7	8.2	42	348	330	32	524	607	36	397	536	0.46	0.32
Slight	13	49.4	8.8	3.7	2.6	13	204	112	12	247	181	11	172	132	0.61	0.40
Moderate	14	44.4	13.0	13.8	2.0	14	286 ^e	157	7	506	433	11	309	223	0.37	0.16
Severe	15	48.0	8.2	22.2	3.9	15	531 ^f	477	13	790 ^g	821	14	639 ^h	780	0.44	0.35
Minor depressive disorder	16	46.7	13.0	10.8	4.6	16	141	84	10	233	221	15	175	191	0.65	0.37
Healthy control subjects	39	46.2	7.2	—	—	32	146	117	34	203	132	38	152	98	0.53	0.33

^aSignificant difference among major depression subgroups, the group with minor depression, and control subjects (Kruskal-Wallis ANOVA $H=25.6$, $df=4$, $p<0.01$).

^bSignificant difference among major depression subgroups, the group with minor depression, and control subjects (Kruskal-Wallis ANOVA $H=14.5$, $df=4$, $p<0.01$).

^cSignificant difference among major depression subgroups, the group with minor depression, and control subjects (Kruskal-Wallis ANOVA $H=14.3$, $df=4$, $p<0.01$).

^dRatings of severity based on scores on Hamilton Rating Scale for Depression: slight, score ≤ 7 ; moderate, score $= 8-17$; severe, score ≥ 18 .

^eSignificant difference from control subjects (Dunn procedure; $Q=2.97$, $K=5$, $p<0.05$).

^fSignificant difference from control subjects (Dunn procedure; $Q=4.38$, $K=5$, $p<0.01$).

^gSignificant difference from control subjects (Dunn procedure; $Q=3.42$, $K=5$, $p<0.01$).

^hSignificant difference from control subjects (Dunn procedure; $Q=3.00$, $K=5$, $p<0.05$).

Among the psychiatric patients, 29 of the 42 patients with major depressive disorder and seven of the 16 patients with minor depressive disorder had been treated with psychotropic drugs (tricyclic or tetracyclic antidepressants, sulpiride, or benzodiazepine derivatives) when the saliva was collected. The remaining patients had not taken psychotropic drugs for at least 30 days before the sampling of saliva. None of the patients or control subjects had taken nonsteroidal anti-inflammatory drugs for at least 1 week before the sampling of saliva.

After the mouth was washed out thoroughly, unstimulated whole saliva was collected into an Eppendorf 1-ml pipette tip and transferred to a sterile polystyrene tube as previously reported (9). The time required for its collection was measured in each case. The rate of saliva flow was measured in milliliters per minute. To minimize the effect of circadian changes in salivary prostaglandin levels (12), the saliva was collected before lunch between 10:00 a.m. and 12:00 noon. It was immediately frozen and was stored at -20°C . The storage time of saliva before extraction of prostaglandins was less than 7 days.

The assay was carried out blindly with respect to the diagnoses and the clinical status of the subjects. After extraction of prostaglandins, we quantified the amounts of PGD₂, PGE₂, and PGF_{2α} by means of radioimmunoassay. The extraction and radioimmunoassay procedures used are described in our previous article (9). Extraction of prostaglandins was carried out at $0-4^{\circ}\text{C}$ according to the method of Powell (13) with the following modifications: immediately after the saliva (2–10 ml) was thawed, 20 ml of 15% ethanol was added, and the mixture was then acidified to pH 3–4

with 1 M HCl. After the mixture was centrifuged at 1,500 g for 20 minutes, the supernatant was applied to a SEP-PAK C 18 cartridge (Water Associates, Boston). The SEP-PAK cartridge was washed with 20 ml of 15% ethanol followed by 20 ml of hexane. The prostaglandins were then eluted with 10 ml of ethyl acetate. Ethyl acetate eluates were evaporated to dryness and stored at -80°C until radioimmunoassay could be performed. Recovery rates were monitored with [³H]prostaglandins; the mean recovery rates of PGD₂, PGE₂, and PGF_{2α} with the aforementioned extraction procedure, were 76%, 84%, and 90%, respectively. Specific antisera for PGD₂, PGE₂, and PGF_{2α} were obtained according to the methods described by Jaffe and Behrman (14). The concentrations needed to inhibit 50% of the total radiolabeled prostaglandin binding for PGD₂, PGE₂, and PGF_{2α} under the standard assay conditions were 452 pg, 452 pg, and 278 pg, respectively. The inter- and intra-assay variation coefficients of these assays were below 9.8%. The cross reactivities of the anti-PGD₂, -PGE₂, and -PGF_{2α} antisera to the other two prostaglandins were less than 1%, 4%, and 4%, respectively.

The data were analyzed with the Kruskal-Wallis one-way analysis of variance, Dunn procedure, and Pearson's correlation.

RESULTS

As shown in table 1, the patients with major depressive disorder had higher PGD₂, PGE₂, and PGF_{2α} levels than the healthy control subjects. The differences between groups were consistent among the three pros-

aglandins; i.e., significant positive correlations were obtained for PGD_2 versus PGE_2 ($r=0.80$, $df=35$, $p<0.01$), PGE_2 versus $\text{PGF}_{2\alpha}$ ($r=0.94$, $df=27$, $p<0.01$), and $\text{PGF}_{2\alpha}$ versus PGD_2 ($r=0.86$, $df=35$, $p<0.01$).

Table 1 also shows that the salivary prostaglandin concentrations became higher as the severity of depressive illness increased. The salivary PGD_2 , PGE_2 , and $\text{PGF}_{2\alpha}$ concentrations of the severely depressed group were significantly higher than those of the healthy control subjects. The PGD_2 level of the moderately depressed patients was also significantly higher than that of the control group. There was no significant difference between the slightly depressed group and the control subjects. Furthermore, we found significant positive correlations between salivary prostaglandin concentrations and the severity of depressive illness in the patients with major depression (PGD_2 : $r=0.46$, $df=41$, $p<0.01$; PGE_2 : $r=0.54$, $df=31$, $p<0.01$; $\text{PGF}_{2\alpha}$: $r=0.45$, $df=35$, $p<0.01$). On the other hand, the rate of saliva flow in the patients with major depressive disorder was comparable to that of the control subjects. Furthermore, there was no significant correlation between the severity of depressive illness and the saliva flow rate in the patients with major depression ($r=-0.28$, $df=41$). In contrast to the findings in the patients with major depression, the salivary prostaglandin concentrations of the patients with minor depression, who showed moderately high Hamilton depression scores, were within the levels of the healthy control subjects. No significant difference was observed in salivary prostaglandin concentration or saliva flow rate between the medicated and nonmedicated patients in each diagnostic group or subgroup.

DISCUSSION

Several lines of experimental evidence demonstrate methodological difficulties in the precise determination of prostaglandins. Prostaglandins are easily synthesized by various physical or chemical stimuli at the time of sampling and measurement (15, 16). It is difficult to determine the physiological levels of prostaglandins in plasma or other tissues (15, 16). Saliva can be collected without any tissue damage. Furthermore, saliva itself does not appear to have systems for prostaglandin synthesis and metabolism. Thus, salivary prostaglandins can be determined precisely with minimal interfering factors. It has been thought that prostaglandins are also involved in luteolysis and menstruation (17). The salivary prostaglandin concentrations of females may fluctuate during the menstrual cycle, so we limited our subjects to males.

In our earlier study (9), patients with major depressive disorder who were in the depressive phase had significantly higher salivary prostaglandin concentrations than healthy control subjects. The depressed patients in the current study were not limited to only those in the depressive phase, but the patients with major depressive disorder also had higher salivary

prostaglandin levels than control subjects. Furthermore, among the patients with major depression, salivary prostaglandin concentrations tended to be higher with more severe depression. These results suggest that salivary prostaglandin concentrations reflect the state of major depression.

In the previous study (9), we found no significant difference in mean rate of saliva flow between the patients with major depressive disorder and the healthy control subjects. However, salivary prostaglandin concentrations tended to be higher with slower salivary flows in both groups. Thus, we further demonstrated that the prostaglandin levels in these two groups were clearly distinguished at each saliva flow rate, and we could exclude the influence of differences in saliva flow rate (9). In this study, we found no significant correlation between the severity of depressive illness and the rate of saliva flow. Several investigators have studied saliva secretion in depressed patients by measuring the unstimulated whole saliva. A relationship between slow saliva flow and more severe depression was reported in some earlier studies (18, 19). However, several arguments critical of those findings have arisen (20–22); those investigators used cotton rolls placed in the mouth to collect saliva. In our study, we collected saliva from the mouth into a sample tube. Although there is a difference in the methods of saliva collection, our present findings on saliva flow rate are consistent with the results of the latter studies (20–22). These results suggest that abnormalities in salivary prostaglandin levels in patients with major depression are not caused by abnormalities in the rate of saliva flow.

We also measured the salivary prostaglandin concentrations of patients with minor depressive disorder. Although their Hamilton depression scores were comparable to those of the patients with major depressive disorder who were moderately depressed, there was a large difference in salivary prostaglandin levels between these two groups (table 1). Therefore, we compared the mean scores of the two groups on each item of the Hamilton scale. The mean scores on work and activities, depressed mood, and genital symptoms were significantly higher in the moderately depressed patients with major depressive disorder, while the mean score on hypochondriasis was significantly higher in the patients with minor depressive disorder. Our present results suggest the possibility that major depression, as defined by the RDC, can be distinguished from minor depression by clinical and some biological aspects.

We observed that salivary PGD_2 , PGE_2 , and $\text{PGF}_{2\alpha}$ concentrations increased in a similar manner depending on the severity of depressive illness. Lieb et al. (7) demonstrated high amounts of both PGE_2 and thromboxane B_2 in the plasma of depressed patients. Considering that report with the present results, we can speculate that abnormalities in the arachidonic acid cascade may be associated with depression.

In our previous study (9), no significant difference in salivary prostaglandin concentrations was observed

between medicated and nonmedicated groups with major depressive disorder. Moreover, in this study, we found no significant difference between the medicated and nonmedicated patients with major depression at each severity level, indicating that salivary prostaglandins reflect the depressive state even under the influence of antidepressant medication. Several in vitro pharmacological studies have demonstrated that tricyclic antidepressants inhibit prostaglandin synthesis (23, 24). However, the effect of these drugs on the metabolism of prostaglandins in vivo is not well-known and remains to be studied.

We found that salivary prostaglandin concentrations reflect the state of major depression. However, we cannot rule out the possibility that high salivary levels of prostaglandins are epiphenomena of the development of depression. Nevertheless, considering the many physiological actions of prostaglandins in various organs, it seems likely that they play important roles in the manifestation or modification of some symptoms of major depression.

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The Psychiatric Emergency Service Holding Area: Effect on Utilization of Inpatient Resources

Paulette M. Gillig, M.D., Ph.D., James R. Hillard, M.D., John Bell, M.D.,
Henry E. Combs, A.C.S.W., Caroline Martin, M.S.S.W., and James A. Deddens, Ph.D.

This study compared the rates of hospitalization from two psychiatric emergency services which were similar except that one service had an extended evaluation unit, or holding area, allowing up to 24 hours of evaluation. The rate of hospitalization from the service with the extended evaluation unit was 36%; the rate from the other service was 52%. The difference in admission rates was related to the availability of the extended evaluation unit, which made it possible for many patients to avoid rather than merely postpone admission to the hospital. Clinical determinants of admission and of successful treatment in the unit were also reviewed.

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A primary function of psychiatric emergency services is to decide whether patients are to be treated on an inpatient or an outpatient basis. Some emergency services must make this decision immediately or, at most, within a few hours. Others have the option of "holding" a patient for an extended evaluation—up to 24 or even 72 or more hours—before being forced to make a definitive referral (1-4). If the extended evaluation capacity allows for appropriate referral to outpatient treatment of some patients who would otherwise be referred for inpatient treatment, then this holding capacity is probably worth its cost to the mental health system. If the emergency service holding area does not reduce hospitalization, the resources expended on such a service might be better spent elsewhere in the generally underfunded mental health system. The present study attempted to assess the effect of a 24-hour holding service on the rate of hospitalization by comparing two services which were similar except

that one had the capacity to observe and evaluate patients for as long as 24 hours, whereas the other did not.

METHOD

At the time of this study, the psychiatric emergency service at Humana Hospital-University of Louisville, Ky., did not have a holding area for extended evaluation, whereas the service at the University of Cincinnati did. Otherwise, the two services were very similar. Each psychiatric emergency service served as the primary emergency evaluation center for psychiatric patients referred from a catchment area of more than 1,000,000 persons in an Ohio Valley urban area. Each was associated with a major university medical center, each functioned as the primary point of entry into a state hospital system, and each had more than 600 patient visits per month. Staffing patterns at the two services were similar. In addition, each community had a similar array of community services for the mentally ill, and each had enough hospital beds so that patients assessed as requiring hospitalization could always be admitted.

During the month of June 1986, data were collected for 2½ weeks at Cincinnati and for 4 weeks at Louisville on each patient visit by all patients 18 years of age and older. Demographic data were collected, and patients were asked about recent environmental stressors, bereavement, previous treatment for psychiatric illness or substance abuse, previous suicidal or assaultive behavior, court referral, and the strength of their social support networks (5-11). For each patient placed in the extended evaluation unit at Cincinnati, the primary therapist also made a judgment about what the immediate disposition (i.e., hospitalization or discharge from the psychiatric emergency service) would likely have been for that patient if an extended evaluation area had not been available. The therapist also indicated in what way the extended evaluation unit had been useful in that case. For each patient seen at Louisville, the primary therapist judged whether or not the availability of an extended evaluation unit would have been useful, and in what way. *DSM-III* diagnoses on axes I and II were recorded for all pa-

Received Jan. 19, 1988; revision received Aug. 2, 1988; accepted Aug. 31, 1988. From the Departments of Psychiatry and Mathematics, University of Cincinnati, and Humana Hospital-University of Louisville and Central State Hospital, Louisville, Ky. Address reprint requests to Dr. Gillig, Department of Psychiatry, University of Cincinnati Medical Center, 231 Bethesda Ave. (ML 559), Cincinnati, OH 45267.

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tients. The presenting symptoms of each patient were rated by the primary therapist along the 18 dimensions of the Brief Psychiatric Rating Scale (BPRS) (12).

Completed questionnaires were obtained for 435 consecutive patient visits at Cincinnati and 348 consecutive patient visits at Louisville. Staff members at each site were trained in the use of the questionnaires, but studies of interrater reliability between sites were not conducted.

It was hypothesized that hospital admission rates at Cincinnati would be lower than at Louisville, and it was predicted that therapists at Cincinnati would be able to identify and characterize specific patients treated and released from the extended evaluation unit who would have been hospitalized if the unit had not been available. Therapists at Louisville, on the other hand, were expected to be able to identify and characterize patients who probably would not have been admitted to the hospital if a 24-hour extended evaluation unit had been available. It also was expected that there would be a higher proportion of early discharges from Central State Hospital in Kentucky, to which University of Louisville patients were admitted, than from Rollman Psychiatric Hospital in Ohio, which receives patients from the University of Cincinnati.

RESULTS

Data were collected on marital status, gender, race, and employment status of the patients seen at both sites in order to determine to what degree the samples were comparable. No significant differences were found on the dimensions of marital status, gender, and race. However, a higher proportion of the patients seen at Louisville were employed (38% of the 348 at Louisville; 24% of the 435 at Cincinnati; $\chi^2=12.90$, $df=1$, $p<0.001$).

Patients at both sites were placed most frequently in the same three major diagnostic categories: affective disorders (36% at Cincinnati; 51% at Louisville), psychoses (32% and 36%, respectively), and substance abuse (31% and 14%). The diagnosis of major affective disorder was made more frequently at Louisville than at Cincinnati ($\chi^2=22.90$, $df=1$, $p<0.001$), whereas the diagnosis of adjustment disorder with depressed mood was made more frequently at Cincinnati ($\chi^2=4.77$, $df=1$, $p<0.05$). A recent crisis in a patient's life also was indicated more frequently at Cincinnati (38%) than at Louisville (28%) ($\chi^2=7.53$, $df=1$, $p<0.006$); this may have been related to the higher frequency of the diagnosis of adjustment disorder at Cincinnati.

Substance abuse was diagnosed more frequently at Cincinnati ($\chi^2=45.50$, $df=1$, $p<0.001$), although substance abuse was also one of the three most frequent diagnoses at Louisville. Patients hospitalized at Cincinnati also had substance abuse as "part of the current problem" more often than did their counterparts at

TABLE 1. Disposition of Patients at an Emergency Service With and a Service Without an Extended Evaluation Unit

Disposition	Patients at Service With Extended Evaluation Unit (Cincinnati) (N=435)		Patients at Service Without Extended Evaluation Unit (Louisville) (N=348)	
	N	%	N	%
Released immediately	145	33	167	48
Treated in unit, then released	134	31		
Hospitalized immediately	42	10	181	52
Treated in unit, then hospitalized	114	26		
Total hospitalization ^a	156	36	181	52
Hypothetical hospitalizations if Cincinnati had no unit and Louisville had a unit				
Staff estimate of difference	+65	+15	-36	-10
Total	221	51	145	42

^aSignificant difference between groups ($\chi^2=24.0$, $df=1$, $p<0.001$).

Louisville (38% versus 29%; $\chi^2=6.22$, $df=1$, $p<0.013$).

As predicted, the psychiatric emergency service having access to a 24-hour extended evaluation unit (i.e., Cincinnati) had a significantly lower hospitalization rate (36%) than did Louisville (52%) (see table 1). When therapists at Cincinnati were asked to indicate which of the patients treated and released from the extended evaluation unit would have been hospitalized if the unit had not been available, 65 patients of 134 were placed in that category. Thus, without the extended evaluation unit, the Cincinnati hospitalization rate would have increased to 51%, which is very close to the actual rate at Louisville (52%). Conversely, at Louisville, when therapists were asked to estimate whether or not a patient whom they had hospitalized could likely have been treated and released from an extended evaluation unit, 36 of 181 patients were placed in that category, which would have decreased the hospitalization rate at Louisville from 52% to 42%.

To determine whether more seriously ill patients were being seen at Louisville, resulting in a spurious inflation of the difference in hospitalization rates between the two sites, a two-way factorial analysis of variance was performed. No interaction between the evaluation sites (Cincinnati versus Louisville) and patient outcomes (hospitalization versus release) was found ($F=0.16$, $df=1$, 752, n.s.), and, as expected, at both sites the more seriously ill patients were hospitalized ($F=190.70$, $df=1$, 752, $p<0.0001$). The mean BPRS scores at Cincinnati were higher than those at Louisville for both hospitalized and released patients ($F=13.24$, $df=1$, 752, $p<0.0003$), even though the hospitalization rate was lower.

Therapists at both sites were asked to indicate the purpose for which they used or would have used the extended evaluation unit. The results at Cincinnati and

Louisville were quite similar. The five most frequent cases found (at Cincinnati) or projected (at Louisville) for the extended evaluation unit were assessing suicide potential (56% and 44%, respectively), gathering further history (56% and 45%), assessing dangerousness (50% and 40%), ensuring medical stability (49% and 41%), and linking with other agencies or finding alternate placement (41% and 42%).

Therapists at Cincinnati also found the extended evaluation unit very useful for determining whether a drug- or alcohol-induced organic brain syndrome would clear (39%), although estimates of this use by the therapists at Louisville were not as high (26%). The utilization rate of the unit at Cincinnati for rapid tranquilization of patients was 20%, which corresponded closely to the Louisville therapists' predicted rate (22%).

A comparison was made between University of Cincinnati patients who were referred to the extended evaluation unit for treatment before a decision about hospitalization was made and patients who were not referred to the unit. Forty-two (22%) of the 187 patients not referred to the unit were hospitalized immediately. Eight (4%) were referred directly back to a supervised group home or to an emergency 2-week halfway house. The other 137 (73%) returned home either alone or accompanied by family or friends.

Of the 248 patients treated in the extended evaluation unit, 46% ultimately required hospitalization, 5% were referred to a supervised group home, and 50% returned home either alone or accompanied by family or friends.

Contrary to predictions, a follow-up of the patients who were hospitalized at state hospitals revealed no differences between the sites in the proportions of these patients released within 4 court days ($\chi^2=0.19$, $df=1$, n.s.) and 6 court days ($\chi^2=0.03$, $df=1$, n.s.).

DISCUSSION

This study supported the hypothesis that the availability of a holding area or extended evaluation unit can reduce hospitalization rates. The psychiatric emergency services at the University of Cincinnati and the University of Louisville serve similar populations. The rate of hospitalization was lower at Cincinnati, which has an extended evaluation unit. The Cincinnati staff's estimate of the probable rate of hospitalization if a holding area had not been available (51%) converges with the actual rate of hospitalization at Louisville (52%). The Louisville staff's estimate of the probable rate of hospitalization if an extended evaluation unit had been available (42%) is close to the actual rate of hospitalization at Cincinnati (36%).

Having said this, we hasten to add an important caveat. A holding area will accomplish little toward reduction of hospitalization rates or improvement of patient care in any system where there are not sufficient inpatient beds for patients who really need them.

In such a system, seriously ill patients who need to be admitted will be detained in a holding area for inappropriately long periods because they are too ill to be released. The extended evaluation unit then becomes a de facto hospital ward, although it is poorly equipped for such use. Holding areas help, but they should not be provided in lieu of needed inpatient services.

Another potential criticism of holding areas is the belief that treatment there simply postpones hospitalization rather than avoiding it. To test this hypothesis, the 134 patients who were treated and released from the extended evaluation unit at Cincinnati were followed for the next 30 days. Within this time period, only 10 (7.5%) were admitted to a psychiatric facility—six to the state hospital and four to private hospitals. This supported the view that treatment in the extended evaluation unit did in fact avoid hospitalization in a number of cases.

Some authors (13–18) have recently attempted to analyze mental health systems from an economic standpoint, although others (19) have pointed out the difficulties and potential pitfalls in comparing hospitals along the dimensions of mean or median length of patient stay. Since the present study did compare two treatment centers, caution must be observed when drawing conclusions about the effectiveness of the extended evaluation unit even though known demographic characteristics were similar, because unknown confounding variables could have been operating. However, within these constraints, it does appear that the availability of an extended evaluation unit (holding area) in a psychiatric emergency service can be an effective adjunct to good patient care and that it may also reduce overall costs to the mental health system, particularly in view of the unexpected finding that, once hospitalized, patients were unlikely to be discharged within 1–4 court days.

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Doxepin as an Adjunct to Smoking Cessation: A Double-Blind Pilot Study

Neil B. Edwards, M.D., Joseph K. Murphy, Ph.D., Anna D. Downs, Ph.D.,
Bette J. Ackerman, Ph.D., and Ted L. Rosenthal, Ph.D.

In a double-blind study, 19 adults received bedtime doses of either 150 mg of doxepin hydrochloride (N=9) or placebo (N=10). After 3 weeks the subjects were instructed to stop smoking and continue taking medication for 4 additional weeks. Cessation was reported by all nine doxepin subjects 1 week after cessation and by seven doxepin subjects 9 weeks after cessation. One placebo subject reported cessation. Cotinine assays generally confirmed cessation but were subject to interpretation. Doxepin assays suggested that the precessation level was associated with cessation. Further studies with larger samples and extended follow-up are needed to determine the reliability of these results.

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Although smoking is the chief single avoidable cause of death in our society (1), effective means of sustained abstinence from smoking remain elusive. Because of nicotine's role in maintaining cigarette use and its pervasive physiologic effects (2), simple replacement therapy, e.g., nicotine gum, offers intuitive appeal and has been shown to be effective for some smokers (3, 4). Additional pharmacologic aids have received limited examination (5, 6). Despite similarities between the symptoms of nicotine withdrawal and depression, e.g., drowsiness, concentration problems, irritability, and increased appetite (*DSM-III-R*), we are aware of only two studies that have examined the utility of antidepressants as an aid to smoking cessation (7, 8). The results were contradictory, and both relied on unsubstantiated self-reports of medication use and smoking cessation. Problems associated with self-reports of cessation and adherence to medical recommendations and with various biochemical measures

of smoking have been amply documented (9-11). To clarify previous research and reduce methodologic shortcomings, we undertook the present double-blind pilot study.

METHOD

Subjects were recruited through campus notices and local newspaper and television coverage. Nineteen adults met the following eligibility criteria: 1) age of at least 18 years, 2) a previous smoking cessation failure that was accompanied by withdrawal symptoms, 3) an absence of psychiatric complaints and contraindications for doxepin use, e.g., present or planned pregnancy, use of monoamine oxidase inhibitors, or excessive alcohol use, and 4) a \$135 deposit, which was fully refunded if the subject stopped smoking for 7 days and attended all appointments.

Before enrollment, all procedures were explained and informed consent was obtained. The protocol was approved by the institutional review board for human research. At the first appointment, the schedule for medication, cessation, and subsequent appointments was reviewed. Assignment to the medication condition, doxepin or placebo, was based on a table of random numbers and determined before enrollment. The investigator who made the assignments had no contact with the subjects, and the codebook was not available to the investigators who treated the subjects. Nine subjects were assigned to doxepin and 10 to placebo.

Medication use began the evening of the first appointment (day 1) according to the following schedule: days 1-3, one capsule; days 4-6, two capsules; days 7-49, three capsules. The appearance of the doxepin capsules, which contained 50 mg of active drug, was identical to that of the placebo capsules. All medication was to be taken at bedtime. The medication bottles contained 30 capsules each and were exchanged at the weekly appointments. After the first appointment, each subject met with one of the investigators for 11 brief (15-30 minutes) weekly appointments. The purposes of these appointments were to enhance protocol adherence, to draw blood for laboratory procedures, to monitor medication side effects, and to provide encouragement and support for cessation efforts.

Received Feb. 25, 1988; revision received Aug. 2, 1988; accepted Sept. 1, 1988. From the Department of Psychiatry, University of Tennessee College of Medicine. Address reprint requests to Dr. Edwards, Department of Psychiatry, University of Tennessee College of Medicine, 66 North Pauline St., Memphis, TN 38105.

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Smoking cessation was to start on the morning after the fourth appointment, i.e., day 22. If the subject had not yet stopped smoking at the fifth appointment, a second cessation date was set for the following morning. Thus, some subjects were seen for 13 weekly appointments rather than the planned 12. Subjects who reported failure to stop smoking by the sixth appointment were discontinued from the study; their deposits were forfeited.

Blood samples for cotinine analysis were obtained at the first appointment (pretreatment) and at the fifth appointment (1 week postcessation). Samples for doxepin assays were obtained at the fourth appointment (just before cessation) and at the seventh appointment (discontinuation of medication). All subjects provided blood samples for the doxepin assays. Subjects who reported that they were still smoking were not evaluated for cotinine at the postcessation appointment. Sampling for subjects who required a second cessation date was correspondingly delayed 1 week. The plasma was separated and stored at -20°C for later analysis of cotinine and doxepin. Cotinine was assayed by means of a modification of the radioimmunoassay procedure of Langone et al. (10) with a specific antiserum produced by injection into rabbits of *trans*-4-carboxycotinine bound to albumin. The inter- and intra-assay variations were less than 6%, and the sensitivity was 1 ng/ml (personal communication, American Health Foundation, Valhalla, N.Y.). Doxepin levels were determined by means of gas chromatography-mass spectrometry with a selected ion monitoring method (12). The calculation was based on the ratio of the peak area of doxepin to an internal standard of amitriptyline, which was compared to the ratio of internal doxepin and amitriptyline standards. The inter- and intra-assay variations were 10%, and the detection limit was 10 ng/ml. The laboratory results were not available until after the study's completion.

Statistical analyses were conducted with SAS computer programs (13). Chi-square comparisons of medication conditions were corrected for continuity. All comparisons were two-tailed.

RESULTS

The pretreatment characteristics of the doxepin and placebo subjects were comparable (see table 1). However, the doxepin group contained six women and three men, and the placebo group contained six men and four women. Reports of pronounced side effects prompted further evaluation of two subjects and breaking of the code. Before cessation, one placebo subject was found to be under intermittent psychiatric care for an affective disorder. After cessation, one doxepin subject exhibited high blood pressure. With both subjects, the appointments were discontinued, although telephone contact was maintained. Their data are reported when applicable.

TABLE 1. Pretreatment Characteristics of Smokers Who Received Doxepin (N=9) or Placebo (N=10) as an Adjunct to Smoking Cessation

Characteristic	Doxepin		Placebo	
	Mean	SD	Mean	SD
Age (years)	40.4	10.1	40.5	6.1
Weight (lb)	162.2	42.8	187.1	44.7
Education ^a	5.6	1.0	5.4	1.0
Income ^b	3.6	1.4	2.9	1.4
Cigarettes/day	38.0	12.0	37.0	12.0
Nicotine/cigarette (mg)	0.64	0.22	0.86	0.22
Previous cessation attempts	4.9	4.7	3.3	1.0
Precessation cotinine (ng/ml)	283.9	174.9	235.7	80.0
Tolerance ^c	6.7	1.3	7.5	1.2

^a1=kindergarten-6th grade, 2=7th-9th grade, 3=10th-11th grade, 4=12th grade, 5=some college, 6=college graduate, 7=postgraduate.

^b1=\$0-10,000, 2=\$10,000-\$20,000, 3=\$20,000-\$30,000, 4=\$30,000-\$40,000, 5=\$40,000+.

^cFrom the Fagerstrom Tolerance Questionnaire (14); a score of 7+ indicates high tolerance.

Smoking cessation of 1 week's duration was reported by all of the nine doxepin subjects and one of the 10 placebo subjects ($\chi^2=11.99$, $df=1$, $p<0.001$). Postcessation cotinine levels were undetectable in the one placebo subject and five of the nine doxepin subjects. Of the other four doxepin subjects, one had no blood drawn for the postcessation test and three had detectable cotinine levels. When we used the most stringent cessation criterion of an undetectable cotinine level, the difference in cessation between the doxepin and placebo groups was not significant ($\chi^2=3.0$, $df=1$, $p<0.1$). However, if the time since cessation at the half-life of cotinine, 10-37 hours (10), are considered, one additional doxepin subject may have stopped smoking; his precessation level of 613 ng/ml had fallen to 32 ng/ml 6 days after cessation. Such a reclassification, i.e., consideration of six of the nine doxepin subjects as abstinent, indicated that doxepin was superior to placebo ($\chi^2=5.55$, $df=1$, $p<0.02$). The 20-day delay in sampling another subject does not allow an evaluation of the accuracy of her self-report 1 week after cessation.

By the 12th session (2 months after cessation), two doxepin subjects reported relapse. These two subjects were the only two doxepin subjects who had required a second quit date, and both had had cotinine levels indicative of sustained smoking. According to self-report, the doxepin condition continued to demonstrate more effective cessation ($\chi^2=6.36$, $df=1$, $p<0.02$).

The precessation blood levels of doxepin ranged from undetectable to 32 ng/ml, and a precessation level higher than 10 ng/ml was associated with smoking cessation ($\chi^2=4.10$, $df=1$, $p<0.05$). The two subjects who reported relapse were the only subjects with levels less than 10 ng/ml. The postcessation levels were not associated with outcome. Pill counts were not significantly correlated with pre- or postcessation blood drug levels. Adjusting the correlation for pretreatment weight did not alter the correlation. For the five su

ects who had detectable precessation cotinine levels and took medication for 7 weeks, the pill counts indicated that 83%–98% of the medication had been consumed. Nonetheless, the doxepin levels of three of these five subjects fell from a precessation mean of 19.7 ng/ml to undetectable levels before the doxepin was discontinued.

Both smoking cessation and doxepin use were associated with weight gain. Specifically, the six doxepin subjects who completed the 12 appointments and reported cessation at that time gained a mean \pm SD of 11.7 ± 7.8 lb (range = 4.3–26.2 lb). The one placebo subject who reported cessation gained 2.5 lb. Of the two doxepin subjects who relapsed, one gained 1.2 lb and the other lost 4.5 lb. Comparison of the groups' weight changes from pretreatment to appointment 4 (the last appointment before cessation) indicated a weight gain of 2.0 ± 3.3 lb by the doxepin subjects and a loss of 1.6 ± 2.3 lb by the placebo subjects.

DISCUSSION

To our knowledge, the present study provides the first controlled evidence that antidepressant medication may aid smoking cessation. Because of the small sample size, the data must be considered preliminary. The problems associated with small samples and power (15) are illustrated by the statistical effect of the doxepin subject whose 1-week cessation status could not be confirmed by cotinine assay. Clearly, further studies with larger samples and prolonged follow-up are needed. While the efficacy of doxepin seems apparent, the inefficacy of placebo is not. All subjects had previously failed to stop smoking on their own initiative, and during recruitment for the study it was explicitly stated that medication would be used. Although most subjects reported various side effects and unblinding was necessary with one placebo subject, our impression is that the patient blind may have been insufficient and may have thereby affected the subjects' expectations. Similarly, patient complaints, particularly of dry mouth and drowsiness, or lack of complaints may have subtly altered the investigators' behavior. Unfortunately, we did not systematically assess the adequacy of the blind; the issue of unblinding must be considered in the evaluation of this and other studies (16). Nonetheless, unblinding issues do not negate the superiority of the doxepin condition; the rate of abstinence at the 12th appointment was almost eight times as high in the doxepin subjects as in the placebo subjects (78% versus 10%). In a recent placebo-controlled trial of nicotine gum (3), the subjects' knowledge of their condition did not affect outcome at any point in the year-long study. Although in our study the self-reports at the 12th appointment were not biochemically verified, the possibility that the doxepin subjects lied and the placebo subjects were truthful and thereby forfeited their deposits seems implausible.

The analysis of doxepin levels at the time of cessa-

tion suggested that a threshold level, 10 ng/ml, was necessary for cessation. A clearer understanding of our observations is hampered by the detection limit of our assay procedure and by the omission of desmethyldoxepin assays. Desmethyldoxepin is an active metabolite of doxepin that has a substantially longer half-life. However, doxepin and desmethyldoxepin levels have been shown to be highly correlated at steady-state levels (17). With respect to therapeutic efficacy, the doxepin levels achieved by some of our subjects were comparable to the levels in improved psychiatric patients. However, studies of the relationship between therapeutic efficacy and concentration of doxepin, desmethyldoxepin, or both have shown substantial interindividual variability (17–21). Because the relationship between blood levels of doxepin and outcome for any disorder is not well understood (22, 23), our observation of a threshold level in smoking cessation must be considered interesting but inconclusive. Nonetheless, given the dose and blood levels at the time of cessation, we suspect that in addition to antidepressant effects, some subjects experienced antianxiety effects, which occur earlier than antidepressant effects (19). Our future studies will assess possible changes in levels of anxiety and depression.

Despite a dose (150 mg/day) that is often used with depressed outpatients, maintenance of this dose was sometimes difficult. With the two doxepin subjects who reported relapse, the persistence of unpleasant side effects resulted in titration of the dose such that only 58% and 76%, respectively, of the medication was used, according to pill count. Although the pill counts were unrelated to blood levels, consistent complaints resulting in dose reductions may be a crude index of an inadequate blood level; these two subjects were the only ones with precessation levels less than 10 ng/ml. As with our cessation results, this hypothesis must be examined further with larger samples because previous research (20) has shown the relationship between oral doxepin dose and serum level to be linear.

Another, and perhaps more important, concern in the use of doxepin is weight gain. Several studies (24–26) have examined weight changes during smoking cessation and mechanisms that may be responsible for weight gain. In the present study, cessation by the doxepin subjects was associated with a mean gain of 11.7 lb. We suspect that the weight gain attributable to cessation was probably compounded by weight gain attributable to the use of doxepin (27–29). Although the cardiovascular risk of the weight gained by the doxepin subjects is minor compared to the risk attributable to smoking, evidence suggests that 1) some smokers use nicotine to regulate their weight, 2) fear of weight gain may inhibit cessation attempts, and 3) actual weight gain may be associated with relapse (30–32).

Finally, the mechanism(s) by which doxepin affected outcome must be considered. While the data suggest a pharmacologic basis, the role of expectancy as either an independent or interactive variable cannot be ex-

cluded. The experience of side effects may have provided some confirmation that a subject was receiving the active medication. In addition, both nicotine and tricyclic antidepressants have wide-ranging neuroregulatory effects. Most notably, nicotine has been shown to affect the bioavailability of acetylcholine, β -endorphin, dopamine, and norepinephrine, and these effects may be modulated by the nicotine dose (33). Likewise, doxepin has been shown to affect adrenergic and serotonergic uptake and to block adrenergic, dopaminergic, and cholinergic receptors (34, 35). Given the complex array of potential interactions and the preliminary nature of our investigation, future studies must distinguish among several plausible hypotheses. The increased understanding of the pharmacodynamics of nicotine, antidepressants, and other pharmacologic agents provided by such evaluations may provide new aids to smoking cessation and may thereby enhance the likelihood of achieving the Surgeon General's goal of a smoke-free society by the year 2000.

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Adverse Outcome of Hip Fractures in Older Schizophrenic Patients

Paul E. Yarden, M.D., Marshall G. Finkel, M.D., C.M., Charles S. Raps, Ph.D.,
and James J. Girvan, R.N., C.N.A.

METHOD

The study included all male schizophrenic patients who sustained a fracture of the proximal femur while in psychiatric care at Northport Veterans Administration (VA) Medical Center during a 5-year period from 1981 through 1985. Patients were excluded if they were demented or suffered from severe physical illness that limited mobility. Twenty-one patients, who sustained 26 fractures of the hip, met these criteria; they ranged in age from 51 to 84 years (mean \pm SD = 65 ± 7.4 years). Five patients who subsequently also fractured the contralateral femur tended to be younger (mean age = 58 years). All patients were followed up for at least 1 year after the fractures.

The diagnosis of schizophrenia was made according to *DSM-III* criteria by independent psychiatrists and was well documented in the clinical records. All of these patients had a chronic form of schizophrenia with multiple recurring or consecutive hospitalizations of 15 years or more. When not in mental hospitals, patients were living in community group homes or nursing facilities. The group can be characterized as institutionalized and treated with different antipsychotic medications for many years with limited results. At the time of the fractures all but one were receiving antipsychotic medications, with the majority receiving haloperidol (average dose = 18 mg/day).

The fractures involved the femoral neck or the intertrochanteric areas. Fourteen fractures were intracapsular and 12 were extracapsular. Eighty percent were due to falls, and no cause could be determined for 20%. After the diagnosis of hip fracture was confirmed, patients were transferred to the orthopedic service where orthopedists and physiatrists provided preoperative, surgical, and rehabilitative care. Patients were returned to the psychiatric units only after they were considered surgically healed and without infections.

The mental status of the schizophrenic patients was evaluated with a rating scale constructed for the assessment of chronic psychotic patients (7). It includes nine areas of mental functioning and behavior and is used routinely on our psychogeriatric service; hence, ratings were available on all patients from a period before the fractures occurred. Patients were rated 6 months and 1 year after the fracture, and the results

The psychiatric and ambulatory course of 21 older chronic schizophrenic patients who sustained hip fractures was studied prospectively, and their walking ability after the fractures was compared to that of 25 nonpsychiatric hip fracture patients. Although the schizophrenic patients were younger when the hip fractures occurred, their recuperation and ambulatory outcome were significantly worse. The psychiatric course was assessed with a standardized rating scale that was administered 6 months and 1 year after the fractures and compared to similar ratings done before the fractures. Significant mental deterioration was found at 6 months after the fractures, with no further changes later.

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It has been reported that hospitalized psychiatric patients suffer more frequently from hip fractures than do normal persons of similar age, with consequent mortality and morbidity greatly increased (1-4). The orthopedic treatment and rehabilitation of these often regressed and uncooperative patients may present unusual difficulties (5, 6) despite modern surgical and rehabilitative procedures aimed at promoting early ambulation.

A review of the literature shows that the relatively few relevant studies are focused mainly on the orthopedic aspects, do not differentiate well between various diagnostic groups of older mental hospital patients, and do not evaluate them from a psychiatric point of view. It was our clinical impression that older schizophrenic patients present specific problems and deserve to be studied as a separate entity.

This prospective clinical study was carried out to investigate the psychiatric and ambulatory outcome of hip fractures in a group of older male schizophrenic patients.

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TABLE 1. Complications Related to Hip Fracture or Surgery in 21 Older Schizophrenic Patients and in 25 Older Control Subjects

Complication	Number of Complications	
	Schizophrenic Group (26 fractures)	Control Group (25 fractures)
Pneumonia	7	2
Pulmonary embolism	2	1
Thrombophlebitis	0	1
Deep wound infection with removal of orthopedic hardware	2	0
Superficial wound infection	6	2
Infected decubitus	9	0
Urinary tract infection	7	2
Urinary incontinence, not previously present	10	0

compared. Two of the authors rated patients separately, and after discussion, differences were resolved.

In order to make comparisons of ambulatory outcome, 25 nonpsychiatric subjects treated for hip fractures on the same orthopedic service during the same time period were retrospectively and randomly selected from the case records. Patients were not included if they had a psychiatric diagnosis, were taking psychotropic medication, or were suffering from severe physical illness that limited mobility before the fractures. The control patients may be described as veterans with various service-connected disabilities who were using the VA hospital also for treatment of any subsequent unconnected medical or surgical illness. They were relatively indigent but were living independently of institutions at the time of the fractures. The mean \pm SD age of the control group was 70 ± 7.2 years. They were older than the 21 schizophrenic patients ($t=2.2$, $df=45$, $p<0.05$, two-tailed).

Surgically, the schizophrenic patients and the control patients received similar treatment. Among the schizophrenic patients, 11 fractures were treated with prostheses, 10 with open reduction and internal fixation, and five with bedrest; among the control subjects the corresponding figures were 10, 13, and two.

Determinations of ambulatory outcome were made 1 year after the fractures. A rating of good outcome was assigned if the patient had no or mild limitation in walking, did not complain of pain, and lost less than 20% of hip motion. A rating of fair outcome was assigned for moderate pain, moderate limitation in walking, and up to 50% loss of hip motion; and a rating of poor outcome was assigned for severe limitation of walking and more than 50% loss of hip motion. Those given a rating of "poor outcome" lost the ability for independent walking, and many became confined to a wheelchair or were bedridden.

RESULTS

Mortality was low, and only one schizophrenic patient died (from pulmonary embolism) shortly after the

TABLE 2. Scores on the Harris Mental State Scale of 20 Older Schizophrenic Patients Before and After Their First Hip Fracture*

Category	Score on Harris Scale				t^b (df=18)
	Within 6 Months Before Fracture		6 Months After Fracture		
	Mean	SD	Mean	SD	
Speech	2.2	0.93	3.0	1.20	4.07 ^c
Mood	1.3	0.47	2.2	0.99	3.85 ^d
Delusions	3.0	0.92	3.4	0.82	2.99 ^d
Hallucinations	2.2	0.99	2.9	1.20	3.13 ^d
Temporal orientation	1.5	0.83	2.6	1.00	5.77 ^c
General information	2.2	0.77	2.9	0.93	3.90 ^d
Feeding habits	1.1	0.31	1.7	0.75	4.07 ^c
Toilet habits	1.5	0.94	2.8	1.33	4.77 ^c
Occupation	3.7	1.03	4.5	0.95	4.66 ^c

*Score range=1-5, with higher numbers representing greater impairment.

^bTwo-tailed t tests for dependent samples.

^c $p<0.001$.

^d $p<0.01$.

fracture. None of the control subjects died in the first year after the fracture.

Table 1 presents the complications related to the fractures and their treatment for the two groups. It can be seen that the schizophrenic patients had many more complications, especially infections.

In the comparisons of ambulatory outcome 1 year after the fractures, schizophrenic patients fared much worse than the control subjects ($\chi^2=21.5$, $df=2$, $p<0.001$). One schizophrenic patient had a good outcome; eight, fair outcomes; and 17, poor outcomes. Among the control subjects, 12 had good outcomes; 11, fair outcomes; and two, poor outcomes. (When we excluded the five patients with contralateral fractures and the one deceased patient in the schizophrenic group, there was still a significant difference in outcome between the two groups [$\chi^2=15.7$, $df=2$, $p<0.001$].)

Table 2 presents the mean of the Harris ratings just before the first fracture and 6 months after the fracture for the 20 schizophrenic patients. As can be seen, after 6 months the schizophrenic patients were rated as being more impaired on all nine categories of the Harris scale. There was no further deterioration or improvement 1 year after the fracture.

Six months after the fracture the schizophrenic patients with poor ambulatory outcome tended to be rated as more deteriorated than those with fair and good outcomes on seven of the nine categories of the Harris scale; however, the differences did not attain significance, possibly due to the small number of patients in the study.

Finally, we looked at the likelihood of contralateral fractures. Among the 20 schizophrenic patients who survived 1 year after the first hip fracture, five suffered a subsequent fracture in the opposite femur. Among the 25 control subjects, none suffered such an additional fracture. This difference is significant ($p<0.02$, Fisher's exact test).

DISCUSSION

Our results suggest that hip fractures have grave consequences for the well-being of chronic schizophrenic patients. Independent ambulation was lost or severely compromised in the majority, further impairment of their mental condition occurred, and they tended to develop chronic, debilitating infections.

Detailed consideration of the orthopedic treatment was not within the scope of this investigation, but it was felt that the schizophrenic patients received competent surgical care, as the generally good results of the nonpsychiatric individuals treated on the same orthopedic and rehabilitation service indicate. It is possible that behavior patterns produced by the schizophrenic illness made their postoperative care and rehabilitation difficult.

Rehabilitation for ambulation training was offered to all patients, but it became a frustrating problem as patients lacked motivation to become independent. They often refused to walk, used assistive devices improperly, got into contraindicated positions, and became hostile toward the therapists, generally discouraging efforts on their behalf and even causing training to be abandoned prematurely. Moreover, several patients who had walked independently 3 months after the fracture later stopped walking and preferred to sit for most of the day, which led to a deterioration of previously improved functional skills.

Peculiar behavior may have also contributed to the slow healing and higher rate of wound infection among the schizophrenic patients. Many picked on sutures and smeared feces, and most did not take care about their personal hygiene.

The appearance of further mental deterioration in the schizophrenic patients after hip fracture has to be interpreted with caution. Although it is possible that the deterioration displayed was associated with advancing age or the disease process, numerous reports suggest a certain stabilization in schizophrenic patients in old age, with no further deterioration or dementia (8, 9).

The schizophrenic patients in our sample were younger at the time of their hip fractures than has been reported for institutionalized patients (1-5) and for the general population in other studies (10, 11) and were younger than our control group. Moreover, those with subsequent contralateral hip fractures were the youngest in the group. Our findings suggest that specific factors associated with chronic schizophrenia or its treatment increase vulnerability at an age that is younger than otherwise anticipated.

Among the various influences reported, which may predispose to bone fragility and trauma, reduced mobility (12, 13), undernutrition (14), and intake of neuroleptic medication (15) may be noteworthy. The schizophrenic patients in our study had been in a state

of physical inactivity for years as a combined result of institutionalization, residing in locked wards, negativism, and catatonic symptoms. They were receiving relatively high doses of neuroleptic medications, which may have contributed to orthostatic hypotension; most of the falls occurred in the early morning hours, and some patients fell in an attempt to stand up from sitting or supine positions. In addition, many patients had dyskinesias and parkinsonism, which may have caused further mobility disturbances. Weight fluctuations were common. In this regard, seven patients were underweight, and three of them sustained fractures in both hips. It is tempting to suggest that osteoporosis (16) may affect chronic schizophrenic patients at relatively young ages, independent of gender differences. A systematic study of bone density, therefore, could contribute further valuable information.

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Relationship Between Endometriosis and Affective Disorder

Edward Walker, M.D., Wayne Katon, M.D.,
Lindy Michael Jones, M.D., and Joan Russo, Ph.C.

Comparing 14 women with and 55 women without endometriosis, the authors found no significant differences in the prevalence of affective disorder. They discuss the discrepancy between their finding and Lewis et al.'s finding of an association between affective disorder and endometriosis.

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A recent report by Lewis et al. (1) described a consecutive sample of 16 patients with laparoscopically proven endometriosis, 12 of whom met DSM-III criteria for a mood disorder. Of the 12, 10 had bipolar disorder and two had major depression. Additionally, nine of the 16 subjects had first-degree relatives with histories of severe mood disorders. After reviewing possible common hormonal similarities between mood disorders and endometriosis, Lewis et al. suggested a possible link between the two disorders. As part of an ongoing study of chronic pelvic pain (2), we obtained a consecutive sample of 69 women who had been examined by laparoscopy. We studied these women to determine the relationship between endometriosis and affective disorder and compared our findings with those of Lewis et al. (1).

METHOD

The subjects were 69 women sequentially selected from the laparoscopy schedules of a university hospital

and an urban obstetrics-gynecology private practice, and all had undergone laparoscopy for evaluation of infertility or pelvic pain or for tubal ligation. Reports of the procedures were rated according to the American Fertility Society Classification for Endometriosis (3) by a gynecologist blind to the patients' psychiatric diagnoses. This classification scores endometriosis or adhesions on a scale of 0 to more than 40 points. We had studied 55 (25 chronic pain patients and 30 control subjects) of these 69 women in an investigation of chronic pelvic pain (2); for the current study, we added 14 chronic pain patients. Thus, 39 women in our current sample had chronic pelvic pain and 30 did not.

Psychiatric evaluations were performed by three trained interviewers, who were blind to the patients' laparoscopy results, using the NIMH Diagnostic Interview Schedule (4) and the Family History Research Diagnostic Criteria (5). In an informal attempt to increase reliability, seven of the interviews were completed by two interviewers, who achieved 100% agreement on psychiatric diagnosis. All 69 women consented to participate in the study.

Data on age, psychopathology scores, and number of first-degree relatives with affective disorder were analyzed with Student's *t* tests and reported as means \pm SD. Data on prevalence of child and adult sexual abuse were analyzed with Fisher's exact test, and data on psychiatric diagnosis, with the exception of bipolar disorder, were subjected to chi-square analysis.

RESULTS

The 14 women with endometriosis and the 55 women without endometriosis did not differ with respect to age (31.9 ± 5.2 and 28.8 ± 6.5 years, respectively; $t=1.87$, $df=67$) and pathology scores (5.2 ± 4.7 and 2.9 ± 5.9 ; $t=1.01$, $df=67$). The number of first-degree relatives with affective disorder diagnoses per patient also did not differentiate the two groups

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TABLE 1. Diagnoses and Personal and Family Histories of 14 Women With and 55 Women Without Endometriosis

Characteristic	Endometriosis				Nonsignificant Analysis
	Present		Absent		
	N	%	N	%	
Bipolar disorder	0	0	3	5	
Major depression					
Current	2	14	12	22	$\chi^2=0.39$, df=1
Lifetime	5	36	22	40	$\chi^2=0.09$, df=1
Alcohol abuse, lifetime	4	29	15	27	$\chi^2=0.01$, df=1
Chronic pelvic pain	7	50	32	58	$\chi^2=0.06$, df=1
Affective disorder in relative ^a	7	50	39	71	$\chi^2=2.20$, df=1
Sexual abuse					
Child (age≤14)	5	38	22	40	Fisher's p=0.51
Adult (age>14)	2	14	19	35	Fisher's p=0.11

Patients with at least one first-degree relative with affective disorder.

0.7 ± 0.9 and 1.3 ± 1.4 , respectively; $t=1.80$, $df=67$). As shown in table 1, we found no significant differences between the groups in the prevalence of bipolar illness, major depression, alcohol abuse, chronic pelvic pain, first-degree relatives with affective disorder diagnoses, and histories of sexual abuse.

DISCUSSION

There are several possible explanations for the fact that unlike Lewis et al. (1), we did not find an association between affective disorder and endometriosis. We selected subjects from laparoscopy schedules whose laparoscopy results were not known by the psychiatric interviewers, whereas Lewis et al. interviewed women with known endometriosis, which could have biased their findings. Our sample included a comparison group, and the Lewis et al. study did not. Also, we selected women from a more diverse pool, including a private practice clinic and a university clinic, which allowed a more heterogeneous mix of patients; the sample of Lewis et al. was drawn from a university clinic that may have had an overrepresentation of patients with psychiatric illness. Almost half of our sample were asymptomatic, undergoing laparoscopy for infertility evaluations or bilateral tubal ligations. These women generally had rates of affective illness no different from those of women in the general population. It is not clear whether the Lewis et al. sample had

gynecologic symptoms. Gath et al. (6) surveyed a community sample of 521 women and found that psychiatric morbidity (most commonly, affective illness) and the personality dimension of neuroticism were significantly related to a wide range of gynecologic symptoms, including dysmenorrhea, premenstrual tension, some symptoms of excessive menstruation, flashes, and sweats. Thus, if the women studied by Lewis et al. had gynecologic symptoms, they might also have had a higher than normal rate of psychiatric illness. Endometriosis is often discovered during laparoscopy in women who have not complained of symptoms. Women with endometriosis who complain of symptoms and seek medical care may have a higher rate of psychopathology. In two studies, one of premenstrual syndrome (7) and the other of irritable bowel syndrome (8), patients with either of these syndromes who sought medical attention could not be differentiated from comparison subjects with similar symptoms who did not seek care by number or severity of symptoms; however, they could be differentiated by the degree of psychopathology, particularly affective illness.

We studied only 14 women with endometriosis and Lewis et al. studied only 16. Well-designed investigations with larger samples of patients are necessary to draw further conclusions about the relationship between endometriosis and affective illness.

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Cocaine Use by Senior Medical Students

Scott Conard, M.D., Patrick Hughes, M.D., DeWitt C. Baldwin, Jr., M.D.,
Karl E. Achenbach, Ph.D., and David V. Sheehan, M.D.

The authors studied 589 senior medical students' attitudes about and use of cocaine. Reported use was 36% in the students' lifetimes, 17% in the past year, and 6% in the past month. Overall, these rates were lower than those of an age-matched cohort.

(Am J Psychiatry 1989; 146:382-383)

To remain alert during long hours of study and hospital duty, roughly half (44% to 54%) of the medical students in the 1960s (1, 2) reported at least some use of amphetamine types of stimulants. Increased legal controls over these substances have been associated with lower rates of reported use (7% to 24%) in the 1970s (3-5). In contrast, the use of cocaine by medical students has shown a dramatic increase (6, 7). Has cocaine replaced amphetamines as the stimulant of choice among medical students?

Before 1984, only one study of medical students mentioned cocaine specifically, reporting that 2% of the respondents had used cocaine, opium, or heroin (8). Since 1984, several authors have reported that "lifetime-ever" use of cocaine among medical students varies between 10% and 39% (6, 7). But generalizing about medical students' cocaine use on the basis of these studies is limited for two reasons. The questionnaires and methods used were different, which makes the results difficult to compare. Second, the study populations were limited to one school, state, or geographic region. In addition, there is a lack of data on medical students' knowledge and attitudes about cocaine. To address these questions, a pilot study on substance use among senior medical students was con-

ducted at 13 medical schools distributed geographically throughout the United States.

METHOD

The study design and substance use questionnaire were based on the National Institute on Drug Abuse's (NIDA's) Monitoring the Future study at the University of Michigan Institute for Social Research (9). Data collected included demographic characteristics, drug use, major sources of drug knowledge, and attitudes about drug use. In the spring of 1986, the questionnaire was anonymously administered to 1,427 senior medical students at 13 American medical schools in the Northeast, Southeast, Midwest, and West. The use of similar questionnaire items and methods permitted a comparison to the results collected in the NIDA study during the fall of 1985 on adults age 25-27 years (9). A more detailed discussion of the questionnaire and methodology is available in the study by Conard et al. (10).

RESULTS

Of 1,427 questionnaires distributed, 589 usable answer sheets were received, for a single contact response rate of 41%. The number of questionnaires returned from each region was nearly equal, ranging from 143 to 153. The individual school return rate ranged from 29% to 72%, with at least one school in each region exceeding 55%, except the West.

Thirty-six percent (N=212) of the medical students reported that they had used cocaine at least once in their lives. Seventeen percent (N=100) had used it in the past year and 6% (N=35) in the past month. Of those who had used cocaine in the past month, three (0.8% of the whole sample) stated that they had used it on more than five occasions. Of the high school graduates in the NIDA survey, 38% reported that they had used cocaine in their lifetime, 23% in the past year, and 10% in the past month. Of the college graduates, 34% reported that they had used cocaine in their lifetime, 20% in the past year, and 8% in the last month. These results show that, with the exception of cocaine use among college graduates (lifetime use of 34% versus 36% for medical students), the percentage

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TABLE 1. Attitudes of 589 Senior Medical Students Toward Occasional and Regular Cocaine Use^a

Response to Questionnaire Item	Occasional Use (once or twice)		Regular Use	
	N	%	N	%
Risk of harm from using cocaine				
None	231	39.2	4	0.6
Slight	255	43.3	36	6.1
Moderate	60	10.2	194	32.9
Great	35	5.9	350	59.4
Disapproval of cocaine use				
Do not disapprove	276	46.9	9	1.5
Disapprove	147	25.0	118	20.0
Strongly disapprove	164	27.9	460	78.1
Recommended consequences for physician users				
None	448	76.1	9	1.5
Require treatment	78	13.2	229	38.9
Suspend license while in treatment	41	7.0	299	50.8
Revoke license	15	2.6	46	7.8

^a"Can't say" and no response not included.

Of medical students who had used cocaine was lower than that of the age-matched cohort in the NIDA study.

The preferred route of administration for medical students was "snorting" (78%, N=165). Other methods included oral (13%, N=28), smoking (5%, N=11), free basing (2%, N=4), and injection (1%, N=2). The major reasons given for taking cocaine were to experiment (60%, N=127), to "get high" (50%, N=106), and to have a good time with friends (48%, N=102). Only 17% (N=36) reported using cocaine to increase energy level, and 10% (N=21) reported using it to stay awake. Of greater significance, perhaps, is the fact that some 18% (N=106) of the subjects indicated that they probably would be using cocaine in some fashion in 5 years. The major source of information on cocaine was written material (36.7%, N=216). Lectures (23.4%, N=138), close friends (17.5%, N=103), and television, film, and radio (12.9%, N=76) were cited as other major information sources.

Most medical students felt occasional cocaine use (once or twice) represented only a slight risk of harm; half did not disapprove of occasional use; and three-fourths would not take action against a physician found to be using cocaine occasionally. In contrast, regular cocaine use was considered by more than 90% to be of moderate or great risk; over three-fourths strongly disapproved of regular use; and nearly 98% would require treatment or revoke or suspend the license of any physician found to be regularly using cocaine (table 1).

DISCUSSION

Over a third of this national sample of medical students had experimented with cocaine, and one in 17 reported use in the past month. Yet, their use of cocaine was lower than that of a national age-matched cohort. The majority of medical students used cocaine to experiment and to "get high" with their friends. Few used cocaine as a stimulant to stay awake or to enhance work or study performance in the manner in which amphetamines were used in the 1960s. Medical student awareness of the dangers of cocaine use is demonstrated in this sample by their lower rate of use than the general population's and by their strong disapproval of regular cocaine use by physicians. Of concern, however, is their leniency with occasional cocaine use and the fact that over 30% relied on close friends and television, film, and radio as their major sources of knowledge about cocaine. To discourage further cocaine use (and possible addiction) by medical students, medical education should be expanded to include coursework on the dangers of cocaine. Possible mechanisms to accomplish this include didactics in courses like pathology and pharmacology and a rotation in the third or fourth year on a substance abuse unit.

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Self-Reported Anxiety in Adolescents

Gail A. Bernstein, M.D., Barry D. Garfinkel, M.D., and Harry M. Hoberman, Ph.D.

In a study of 988 adolescents, female gender, somatic complaints, history of physical and sexual abuse, poor grades, use of street drugs, and family history related to depression were among factors that differentiated adolescents reporting high anxiety from those reporting low anxiety.

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O rvaschel and Weissman (1) reviewed seven community surveys of anxiety symptoms in children and observed that anxiety symptoms were prevalent in children of all ages. Anxiety symptoms were found to be more frequent in females, more common in blacks than in whites, and more frequent in children of lower socioeconomic status than in those of higher socioeconomic status. The present study identified characteristics that may be more commonly associated with anxiety reported by adolescents.

METHOD

In a rural public high school, 1,089 students in grades 9-12 anonymously completed a demographics questionnaire, the Life Events Checklist (2), the Beck Depression Inventory (3), and the Revised Children's Manifest Anxiety Scale (4). The students completed these scales in one session. On the day the surveys were completed, approximately 150 other students were absent and did not participate in the study.

Data on students scoring 6 or more on the Lie scale of the Revised Children's Manifest Anxiety Scale (N=101) were excluded from the analyses. A score at this level on the Lie scale indicates an attempt to give the socially desirable response or suggests defensiveness (5). The students eliminated because of elevated

Lie scale scores did not differ from the remaining students on any demographic variables and did not have significantly different scores on the revised children's anxiety scale ($t=0.89$, $df=1068$, n.s.). After eliminating the students with elevated Lie scale scores, the sample size was 988.

A score of 22 or more on the revised children's anxiety scale (1.5 SD above the mean according to normative data) (5) was selected as indicative of high anxiety. The sample was thus divided into one group of adolescents with high anxiety scores (N=60) and another group with low anxiety scores (N=928). (It should be noted that having a high score on the revised children's anxiety scale is not synonymous with having clinically significant anxiety.)

First, we compared the subjects in the high-anxiety group with the other adolescents. Second, we conducted a matched case control comparison between members of the high-anxiety group and a low-anxiety group (those adolescents who scored less than 10 on the revised children's anxiety scale). Matching was based on age and gender. Although this matching eliminated age and gender as confounding variables, it was not practical to match on other variables, and so the matching had limitations. The cutoff score of less than 10 was chosen to eliminate the moderately anxious students from the comparison. Fifty-five matched pairs resulted (five high-anxiety subjects could not be matched). A discriminant function analysis and a multiple regression analysis were done on the case control comparison.

The existence of gender-based differences in the characteristics associated with reported anxiety was examined. For this, the sample was divided by age and gender. With 1.5 SD above the mean on the revised children's anxiety scale as a cutoff for high-anxiety subjects in each age-gender classification, we identified the most anxious boys and girls at each age level. Separate high-anxiety and low-anxiety groups were then redefined for boys and for girls, and comparisons were made for gender differences.

RESULTS

The prevalence of self-reported anxiety, on the basis of a Revised Children's Manifest Anxiety Scale score of 22 or more, was 6%. Demographic variables, including race, age, grade in school, head-of-household's

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TABLE 1. Characteristics of High School Students Reporting High Anxiety and Those Reporting Low Anxiety

Item	High Anxiety (N=60)		Low Anxiety (N=928)		Analysis		
	N ^a	%	N ^a	%	χ^2	df	p
Personal characteristics							
Minor or chronic physical illnesses ^{b,c,d}	30	51.7	82	9.0	97.80	2	0.0001
History of physical abuse ^{b,c,d}	18	30.5	66	7.2	38.59	2	0.0001
History of sexual abuse ^{b,c}	13	22.0	57	6.2	20.92	2	0.0001
Suicide attempt in past month ^d	8	13.8	27	2.9	15.68	1	0.0001
Use of street drugs ^{b,c}	10	16.9	65	7.0	6.38	1	0.01
Poor grades ^{b,c}	22	36.7	218	23.7	4.42	1	0.04
Use of alcohol ^{b,c}	22	37.9	242	26.4	3.10	1	n.s.
Family history							
Relative received psychotherapy ^{b,c}	24	40.0	219	25.2	5.62	1	0.02
Relative received antidepressants ^c	7	12.1	37	4.2	5.82	1	0.02
Relative made suicide attempt ^c	23	39.0	163	18.3	13.84	1	0.0002

^aNumber of respondents for each item varies because response rate varied from 94% to 99%.

^bSignificant difference in the case control comparison of 55 matched pairs (at least $p < 0.05$).

^cSignificant for girls, based on $N=454$ (at least $p < 0.05$).

^dSignificant for boys, based on $N=523$ (at least $p < 0.05$).

occupation, whether the student had lived outside the home, religion, adoption, single-parent versus two-parent family, and farm versus town residence, did not differentiate between the high-anxiety and low-anxiety groups. However, the high-anxiety group had significantly more girls than the low-anxiety group ($\chi^2 = 27.54$, $df=1$, $p=0.0001$). The individuals in the high-anxiety and low-anxiety groups were differentiated on the basis of selected personal characteristics and family history items, as shown in table 1.

On the Life Events Checklist, students in the high-anxiety group indicated that a mean \pm SD of 3.33 ± 2.39 stressful events had occurred in the past month; the low-anxiety group reported 1.76 ± 2.20 events ($t = -5.34$, $df=986$, $p=0.001$). The stressors in the two groups were similar, with slightly different ranking. These stressors included an increased number of arguments with parents, trouble with a brother or sister, trouble with classmates, receiving failing grades, losing a friend, and breaking up with a boyfriend or girlfriend. In general, self-reported anxiety was not linked to specific stressors but was related to an increased number of stressors.

Since the sample was large, there was the possibility that we would find differences that were statistically significant but not clinically important. However, with the case control comparison ($N=55$ pairs), all of the differences in demographics and selected characteristics were robust enough to persist, with the exception of students' suicide attempts in the past month, relatives who received antidepressants, and relatives with histories of suicide attempts.

A discriminant analysis on the case control comparison showed the following variables (listed in decreasing importance) to be predictors of an elevated score on the revised children's anxiety scale: total Beck inventory score, use of street drugs, history of physical abuse, and presence of multiple somatic complaints (Wilks's $\lambda = 0.39$; $\chi^2 = 100.7$, $df=4$, $p=0.0001$). The sensitivity of classification was 96.4%, the speci-

ficity was 78.2%, and the predictive value was 87.2%. The multiple regression analysis showed that total Beck inventory score and use of street drugs were the most important variables in predicting the anxiety scale score ($R=0.80$, $df=107$, $p=0.0001$). The total variance accounted for was 63%.

A Pearson product-moment correlation between subjects' total scores on the revised children's anxiety scale and the Beck inventory yielded a significant relationship between anxiety and depression in these adolescents ($r=0.59$, $df=922$, $p=0.0001$). The mean \pm SD Beck inventory score for the adolescents with high anxiety was 20.24 ± 9.19 ; for the remaining students it was 6.61 ± 6.78 ($t = -9.47$, $df=43.37$, $p=0.001$).

A comparison of the girls and boys based on an anxiety score 1.5 SD above the mean for each age and sex group indicated that the factors of sexual abuse, recent suicide attempts, use of street drugs, use of alcohol, poor grades, and family history related to depression differentiated the high-anxiety and low-anxiety girls but not the high- and low-anxiety boys (table 1).

DISCUSSION

This study showed that adolescents who reported high anxiety were more likely to be female than male. A number of characteristics associated with the reporting of anxiety by adolescents appeared to be gender-based (table 1).

The study provided evidence for the overlap of anxiety and depressive symptoms on the basis of the correlation ($r=0.59$) between scores on the Revised Children's Manifest Anxiety Scale and the Beck Depression Inventory. This finding is consistent with that of a previous study which demonstrated an overlap of anxiety and depressive symptoms in adolescents with school phobia (6). In addition, girls who reported anxiety had a family history of relatives with depression, supporting the familial association between anxiety and de-

pressive symptoms. The discriminant function analysis and multiple regression analysis again linked anxiety and depression and, in addition, drug abuse, which may represent the adolescent's attempt to treat the underlying anxiety and depression.

It is possible that this study investigated distressed adolescents with multiple symptoms, rather than those with only self-reported anxiety or anxiety and depression. To evaluate this further, studies should be done in which adolescents who score high on self-report measures of anxiety and an equal number of gender-matched control subjects receive structured diagnostic interviews in order to ascertain the number and type of past and present diagnoses. In the meantime, our investigation clearly delineates the factors associated with a high level of self-reported anxiety symptoms in adolescents.

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The Shanghai 800: Prevalence of Tardive Dyskinesia in a Chinese Psychiatric Hospital

Grant N. Ko, M.D., Liang Dong Zhang, M.D., Wen Wei Yan, M.D.,
Ming Dao Zhang, M.D., David Buchner, M.D., Zhen Yi Xia, M.D.,
Richard Jed Wyatt, M.D., and Dilip V. Jeste, M.D.

The authors found that 73 (8.4%) of 866 patients with chronic schizophrenia in the Shanghai Psychiatric Hospital who had been treated with neuroleptics had tardive dyskinesia. This low prevalence rate is possibly ascribable to the use of relatively low doses of neuroleptics.

(Am J Psychiatry 1989; 146:387-389)

Tardive dyskinesia is a well-described adverse effect of treatment with neuroleptics (1). Of considerable interest is how the risk of tardive dyskinesia is related to neuroleptic dose. In the United States, where relatively large doses of neuroleptics are typical, the point prevalence of tardive dyskinesia ranges from 8% to 35% (2). In countries where smaller doses of neuroleptics have been used historically, the point prevalence of tardive dyskinesia is lower (3, 4). China is one country that has historically used relatively low doses of neuroleptics, although, to our knowledge, the point prevalence of tardive dyskinesia in China has not been studied.

The U.S. State Department and the People's Republic of China, through the National Institute of Mental Health and the Shanghai Institute of Mental Health, collaborated on a point prevalence study of tardive

dyskinesia at the Shanghai Psychiatric Hospital in the People's Republic of China. This psychiatric hospital is comparable to a state hospital in the United States. The purpose of the study was to define the point prevalence of tardive dyskinesia in this group of psychiatric inpatients and to evaluate risk factors for this disorder.

METHOD

Three of us (L.D.Z., W.W.Y., and Z.Y.X.) examined all 866 inpatients at the Shanghai Psychiatric Hospital who met Research Diagnostic Criteria (5) for schizophrenia. The Abnormal Involuntary Movement Scale (AIMS) (6) was administered to all patients, and their charts were subsequently reviewed, without knowledge of AIMS scores, for age, sex, weight, and treatment history, including history of side effects. At the outset of the study, 10 consecutive patients were examined by the team of AIMS raters (N=15); their interrater reliability (kappa) (7) ranged from 0.54 to 1.0. Dichotomous data were used: the categories were presence or absence of tardive dyskinesia. A global AIMS score of 2 or greater was a criterion for the presence of tardive dyskinesia. Two raters at a time performed the calculations; lower rates of agreement came early in the training of raters, and better interrater reliability rates came at the end of the training period, when less experienced psychiatrists had become better at discerning mild tardive dyskinesia. The AIMS scores used were a consensus opinion of at least two raters after three separate examinations of the patients during the course of 1 month. The diagnosis of tardive dyskinesia was made on the basis of specific criteria (2, pp. 54-56) as well as an AIMS global severity score of 2 or greater.

Each subject's medication dose was kept constant for at least a month before data were gathered and subsequently throughout the course of the study. This dose was used as the daily neuroleptic dose in mg of chlorpromazine equivalents (2). From the medication data in the charts, we obtained the total amount of neuroleptic as well as the total amount of clozapine administered to each patient.

Both univariate (t tests for interval variables and

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TABLE 1. Age, Sex, Weight, and Treatment History of 866 Chinese Schizophrenic Inpatients With or Without Tardive Dyskinesia

Item	Patients With Tardive Dyskinesia (N=73)	Patients With- out Tardive Dyskinesia (N=793)	Univariate Analysis ^a		Multivariate Analysis ^b (stepwise multiple regression)				
			t	p	Order of Entry Into Equation	R ²	F	df	p
Age (years)			2.3	<0.05	4	0.01	5.6	1, 859	<0.05
Mean	44.6	40.0							
SD	11.4	16.7							
Sex					5	<0.01	4.5	1, 858	<0.05
Number of men	59	582							
Number of women	14	211							
Body weight (kg)									
Mean	63.4	62.9							
SD	10.0	30.0							
Duration of neuroleptic treatment (months)			2.0	<0.05					
Mean	216	181							
SD	113	145							
Number of admissions									
Mean	3.8	3.7							
SD	1.9	2.7							
Acute extrapyramidal symptoms with first neuroleptic treatment			4.1	<0.01	1	0.04	34.2	1, 862	<0.01
Number	25	88							
Percent	34.2	11.1							
Patients with a family history of schizophrenia			2.5	<0.01	2	0.01	11.3	1, 861	<0.01
Number	20	112							
Percent	27.4	14.1							
Neuroleptic dose (mg/day of chlor- promazine equivalents)			2.1	<0.05	3	0.01	5.1	1, 860	<0.05
Mean	386	304							
SD	325	245							
Total amount of neuroleptic (g/day of chlorpromazine equivalents)									
Mean	3157.5	1592.8							
SD	9223.3	2316.9							
Total amount of clozapine (g)									
Mean	85.0	103.2							
SD	116.7	149.5							
ECT									
Number of treatments									
Mean	13.9	6.9							
SD	23.5	13.7							
Number of patients	39	358							
Percent of patients	53.4	45.1							

^aEither a two-sample t test with unequal variance or a t test with equal variance was used as appropriate.

^bLogistic regression and discriminant function analysis were also performed. Their results were qualitatively identical to those of multiple regression and are therefore not reported.

chi-square tests for categorical variables) and multivariate (regression) statistical analyses were used. To reduce the likelihood of spurious chance significance (type 1 error), variables eligible for the regression were limited to potentially causal variables. Because the distribution of the total neuroleptic amount was quite skewed, log transformation was used for the multiple regression. The dependent variable in the multiple regression was the group (tardive dyskinesia versus no tardive dyskinesia). Using the global AIMS score (range=0-4) as the dependent variable resulted in the same variables entering the regression. Logistic regression and discriminant function analysis were also performed.

RESULTS

Of 866 neuroleptic-treated schizophrenic patients 73 (8.4%) were diagnosed as having tardive dyskinesia. Fifty-nine (80.8%) of the 73 patients with tardive dyskinesia were men and 14 (19.2%) were women. The mean±SD daily neuroleptic dose for the entire patient sample was 311.3±254.0 mg of chlorpromazine equivalents. Table 1 lists the univariate and multivariate analyses referred to in the Method section. In the case of the univariate analysis, variables that differed significantly between groups with and without tardive dyskinesia were a history of acute extrapyramidal symptoms on neuroleptic administration, family

history of schizophrenia, daily neuroleptic dose, the duration of neuroleptic treatment, and age. Other variables listed in table 1, including total amount of clozapine administered, were not significantly different between the groups with and without tardive dyskinesia on two-tailed tests.

In the multivariate analysis, variables entering the regression equation were a history of acute extrapyramidal symptoms, a family history of schizophrenia, daily neuroleptic dose, age, and sex. These variables explained 7% of the variance, and the increment in variance explained by each (R^2) is shown in table 1. Daily dose and total amount of neuroleptic were highly correlated (Pearson $r=0.56$, $N=863$, $p<0.001$), and the total amount of neuroleptic entered the regression if daily dose was removed.

DISCUSSION

We found a relatively low (8.4%) prevalence of tardive dyskinesia in a large Chinese psychiatric hospital where the mean daily neuroleptic dose prescribed was also low (311 mg of chlorpromazine equivalents). Although it is customary to use chlorpromazine equivalents when comparing different doses of multiple neuroleptics in a study group of patients, this is not ideal because different neuroleptics may not be equivalent at low versus high doses (in terms of receptor blockade and clinical efficacy). Other limitations to the present study should be mentioned. This was a cross-sectional study of point prevalence of tardive dyskinesia, and we do not know the rate of spontaneous tardive-dyskinesia-like movements in this group of patients; this makes it impossible to calculate the non-drug-related abnormal movements. We also do not know the time of onset of tardive dyskinesia in the patients examined, which makes it difficult to determine the precise daily dose and total amount of neuroleptics administered before development of tardive dyskinesia. In addition, most patients had received more than one neuroleptic during the course of their treatment. Nonetheless, our study is methodologically similar to other investigations of the prevalence of tardive dyskinesia (1, 2, 8). Our finding is consistent with reports from the United States, Japan, and India associating lower prevalence of tardive dyskinesia with the use of smaller amounts of neuroleptics (3, 8, 9). There is thus evidence to support a recommendation for prescribing neuroleptics in the lowest effective doses in order to reduce the risk of tardive dyskinesia.

The relationship between the presence of tardive dyskinesia and a family history of schizophrenia is intriguing and warrants replication in other settings before any explanations can be offered. The fact that

patients with tardive dyskinesia were significantly older than those without tardive dyskinesia is consistent with findings from other studies (1, 2, 8). The greater proportion of men with tardive dyskinesia in the sample is; however, unexpected and may be merely an artifact of the large male preponderance in the total study group.

We did not find a significant association between a higher amount of clozapine use and the lower prevalence of tardive dyskinesia. Clozapine is an atypical neuroleptic that rarely produces acute extrapyramidal side effects and, according to some researchers (10), rarely produces tardive dyskinesia. We could not test the latter hypothesis directly because of the retrospective nature of the study and the use of other neuroleptics at some time during the course of illness in these patients. A future prospective study is planned to address the prevalence of tardive dyskinesia in a study group of Chinese patients treated with clozapine alone for several years.

We should point out that the absolute differences between groups with and without tardive dyskinesia in values on different variables (table 1) were relatively small. This suggests a marked overlap between the two groups as well as an absence of "strong" risk factors that could be identified in a study of this type.

Cross-cultural investigations such as this one are likely to have relevance for the treatment and understanding of tardive dyskinesia in any country.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

AFFECTIVE DISORDERS

The Biology of Depression, edited by J.F.W. Deakin. London, Gaskell (Washington, D.C., American Psychiatric Press, distributor), 1986, 220 pp., £7.50 (paper).

Our understanding of the biology of depression has evolved substantially over the last decade. We have gone beyond the single-neurotransmitter-based deficiency model, such as the catecholamine hypothesis (1), to a more complicated set of data that cannot be fit nicely into any one conceptual model. Norepinephrine, serotonin, and dopamine are all likely involved; receptor activity, endocrine function, and ionic changes must be considered as well. Coming to an understanding of the complexity of the existing data is no simple task for the practicing psychiatrist or, perhaps, for the research-oriented psychopharmacologist. The data base is immense and the lack of a complete structural model makes grasping it all quite difficult.

The Biology of Depression goes a great distance in making the information more comprehensible. It contains the proceedings of a meeting held in 1985 of the Biological Group of the Royal College of Psychiatrists. The participants discussed a version of what might be called the monoaminergic hypotheses for depression.

Beginning with a historical overview of monoamine anatomy and physiology, the volume proceeds to a description of the behavioral functions of the monoamines, as one way of understanding the workings of monoaminergic systems in depression. The chapter by Deakin and Crow nicely reviews the contrasting behavioral functions of catecholamine and serotonin systems. It then discusses other important reciprocal functions of these two monoaminergic systems, a topic further addressed in later chapters. It suggests that diminished catecholamine function could be primary in depression or secondary to an overactive serotonergic system. The authors discuss the fact that theories of serotonin excess in depression might conflict with other theories of serotonin deficiency; they propose that reduced 5-hydroxyindoleacetic acid (5-HIAA), found in some depressed patients, reflects a compensatory response to excessive serotonergic activity.

The second chapter, which stands apart from the rest, provides an excellent review for the initiate or a comprehensive introduction for the novice of the techniques and the concepts involved in the study of the genetics of depression. There is an in-depth discussion of the concept of morbid risk and the use of family, twin, and adoptive strategies. Following this, the authors describe the use of liability-threshold models for understanding the genetics of affective disorders. Finally, they discuss the need for using biological markers in genetic studies.

The middle section of the book focuses on the various biochemical strategies used in the study of depression, including the search for a true biological marker. Most chapters provide both a topic overview and a specific discussion of the particular areas of interest of the authors of each

chapter. Topics covered include postmortem studies of neurotransmitter levels, serotonin neuroendocrinology, serotonin transport and the antidepressants, α_2 receptors in depression, and the sodium pump in manic-depressive psychosis. Chapters by Cowen and Anderson and Checkley et al., in particular, provide extremely rich discussions of the neuroendocrine strategy for the understanding of the biology of the affective disorders. A minor criticism that could be advanced for this middle section would involve the relatively limited discussion of catecholaminergic aspects as compared with serotonergic ones and the relative absence of reference to hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis dysfunction as part of the broader understanding of the biology of affective disorders.

The final section, made up of three chapters, begins with an excellent yet brief review by Paykel and Hale of the treatment of depression. In particular, the subsection on the treatment-resistant patient is quite good, emphasizing the clinical pearl that so-called treatment resistance can often be another term for improper diagnosis. Another excellent chapter, by Green and Goodwin, contains a discussion of how differences in the mechanism of action of antidepressant drugs and ECT can potentially explain biochemical differences in subgroups of depressive patients. The authors suggest that clinical research focusing on the antidepressant response of patient subgroups can point toward the need for particular basic research studies. The last chapter in the section reviews how peripheral autonomic effects of the antidepressant drugs (for example, changes in salivation, sweating, pupillary size, and blood pressure) can lead to a further understanding of the biology of depression and the pharmacology of the antidepressant drugs.

In sum, the volume provides a wide-ranging review of its topic. The informed resident or investigator will find it a useful reference volume that is highly readable and informative.

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ALAN I. GREEN, M.D.
Boston, Mass.

Depression and Mania, edited by Anastasios Georgotas, M.D., and Robert Cancro, M.D. New York, Elsevier, 1988, 648 pp., \$65.00.

This book would be useful as a reference source for clinicians interested in finding out the data base regarding diagnosis and treatment of depression and manic-depressive illness. It would also be useful for residents seeking to find out about the history of these areas and to acquaint themselves with the literature supporting our knowledge regarding de-

ression and mania, and it would be useful to researchers as review of what we know. In contrast to most other multi-authored tomes, most of the chapters in this book are written by the authorities responsible for the contributions in the specific areas. Thus, one has information about cognitive therapy from Aaron Beck, about convulsive therapy from Max Fink, about animal models from William McKinney, and about cyclothymia from Hagop Akiskal. It is to the editors' credit that they were able to assemble such a fine group of contributors and get the book out on time. The most recent reference I could find in the book was 1987, which is comparatively good for a book published in 1988.

The book contains 42 chapters divided into six sections. Section one, the Introduction, describes the history of manic-depressive illness and the epidemiology of the disorder. Section two, Clinical Syndromes, deals with descriptive psychopathology and differential diagnosis. Section three, Etiology, ranges from psychoanalytic models, animal models, and genetics through neurochemistry and neuropsychology. Section four, Treatment, comprises the majority of chapters, discussing treatment of acute depression, maintenance therapy, convulsive therapy, analytic therapy, and other psychological treatments as well as treatment of the medically ill patients. Section five, Special Forms of Depression, contains chapters relating to childhood depression, mourning, and depression and mania in later life. Section six, Assessment, contains two chapters relating to assessment and laboratory tests.

For the most part, the referencing is comprehensive and reflects the many contributors to the subject matter for each chapter. The book is well written and well edited.

We have had a series of books about depression written primarily for the layperson. This volume, edited by Georotas and Cancro, nicely complements the popular books by providing the data base for our understanding of depression and manic-depressive disorder.

DAVID L. DUNNER, M.D.
Seattle, Wash.

Suicide: Clinical and Epidemiological Studies, by Brian Barraclough with Jennifer Hughes. London, Croom Helm, and New York, Methuen, 1987, 185 pp., \$32.50.

It has now been three decades since Robins et al. in St. Louis and Dorpat et al. in Seattle completed landmark studies of consecutive cases of completed suicides. Their focus was clinical diagnosis established primarily through interviews with family members, physicians, and friends of the deceased. Both studies found that mental illness could be demonstrated in over 90% of the cases and that depressive illness and alcoholism were the most common diagnoses. In 1966–1968, a decade after these two works, Barraclough et al. did a comparable study of 100 suicide cases in West Sussex County, Great Britain. Although the diagnostic findings were similar, the Barraclough study added a new dimension by also interviewing a comparison group of 150 people matched with the suicide cases for age, sex, marital status, and area of residence.

Use of the control group permitted the testing of many hypotheses. For example, if terminal illness were a major factor in suicide, Barraclough et al. would have expected to find more terminal illness among the suicide cases than among the control subjects. They did not. If the death of a parent in childhood were a major contributing factor, the suicide group should have experienced more such losses than

the control group. They had not. Significantly more of them than of the control subjects, however, had experienced the recent death of a parent.

Two decades after his original study, Barraclough has published a book based on the study, building on it, and including some subsequent work on suicide. Barraclough begins by stating that there are two major theories of suicide—social theory, associated with Durkheim, and “the mental illness theory based on medical observation.” He states that these theories are in conflict to some extent. This book is largely a factual treatise in support of the mental illness theory.

For 93 of the 100 suicide cases studied by Barraclough et al. there was sound evidence of the presence of mental illness in the period before death. Depression (70 cases) and alcohol (15 cases) were the major diagnoses. For 13 cases, there was more than one psychiatric diagnosis; in 10 cases alcoholism coexisted with depression.

Barraclough believes that many of the social factors described by Durkheim as related to suicide—living alone, being unemployed, or moving frequently, for example—are often the result of mental illness. Bereavement can precipitate a mood disorder in the mentally ill.

Barraclough deals originally and perceptively with the problem of suicide rates. He uses the fact that the suicide rates among people who have emigrated to the United States correspond in relative rank to the rates in their country of origin as evidence of the relative validity of these rates. He further demonstrates that when deaths listed as undetermined (a category that may reflect variations from one country to another in ascertaining suicide) are added to the suicide totals, these rankings do not change.

Barraclough recognizes that more than a diagnosis is needed to explain a suicide. For example, he compares the suicide cases with a principal diagnosis of depression in the original study group with a sample of 318 patients with endogenous depression who had not killed themselves. He found that only three symptoms of depression distinguished the suicidal group from the nonsuicidal group: insomnia, impaired memory, and self-neglect. A history of a previous suicide attempt was also 10 times more common among the suicide cases than among the depressed subjects who did not commit suicide. Barraclough sees the depressed suicide cases as fairly typical of depressed patients except for a “predisposition to suicidal thinking when depressed.”

Barraclough reasons that since depressed mood, whether the result of a depressive illness, alcohol, or schizophrenia, is so often a precursor of suicide, elevation of depressed mood is a prime goal of suicide prevention. Most of the subjects in his original group had seen a doctor shortly before they died and were taking psychotropic drugs; however, these were often of a type and dose that Barraclough considers inappropriate. At times he implies that proper and adequate use of tricyclic antidepressants will be the answer. He also admits to being disappointed that despite remarkable results in treating individual patients with lithium, there is no evidence that suicide has become any less frequent as a result of its use.

He concludes that there is no evidence that any measure involving individual care or counselling can reduce a community's suicide rate. The proven influences on suicide rates (the rates are lower during wartime and higher during economic recession) suggest that we should look for ways of “organizing society in such a way as to minimize suicide.” Such a conclusion may seem strange in a book emphasizing mental illnesses as opposed to social factors as determinants of suicide.

BarracloUGH has some contempt for analyses based on social statistics as opposed to clinical investigation supplemented by individual case studies. The half-page case studies in this book, however, are no more than statements of a few key facts and listings of symptoms in narrative form.

If sociologists can complain of being unfairly dismissed in this book, those interested in the psychology or psychodynamics of suicide can complain of being totally ignored. For example, BarracloUGH dismisses the suicide notes left by the patients he studied as not providing useful information. Studies have demonstrated, however, that such notes provide a wealth of meaningful insights into the patient's motivation for suicide. BarracloUGH's statement that depressive patients who kill themselves are more prone to suicide when depressed seems to be a tautology raising more questions than it answers. Since the original study of BarracloUGH et al., tricyclics have been prescribed more often and in adequate doses, and clinicians are seeing more patients who kill themselves while overtly less depressed. Perhaps reducing depression is analogous to reducing fever: it is important but not necessarily curative if the underlying condition has not been dealt with.

It would be a mistake to dismiss *Suicide: Clinical and Epidemiological Studies* for these shortcomings. The work is a sound, original exposition of a particular method, a method that remains one of the valuable ways we have of gathering factual information about suicide. No one has used the method more persuasively and more effectively than has BarracloUGH, and this book is, in my opinion, one of the more important works on suicide to be published in recent years.

HERBERT HENDIN, M.D.
New York, N.Y.

Cerebral Hemisphere Function in Depression, edited by Marcel Kinsbourne, M.D. Washington, D.C., American Psychiatric Press, 1988, 190 pp., \$15.95.

This book is a collection of data from symposiums and new research sessions at APA annual meetings. This volume is an addition to the Progress in Psychiatry series sponsored by the American Psychiatric Press. The intent of the series is to present compact books on timely research topics that "examine in detail the newest information about a developing aspect of psychiatry" (p. ix).

In his introduction, Dr. Kinsbourne says, "A surge of interest in biological psychiatry has swept into prominence a new era of scientific endeavor: the neuropsychology of psychopathology" (p. xi). This book focuses on cerebral function and/or dysfunction in affective disorders with a special emphasis on depression. The idea that cerebral dysfunction could be a marker for psychopathology arose from the observation that symptoms of structural and functional cerebral disorders often mimic each other. A major research effort on the cerebral basis of emotion has provided "normative underpinnings" for such an approach. Evidence is very rapidly accumulating that various areas of the cerebral cortex play roles in controlling psychiatrically relevant behavior. Examples include the involvement of the frontal lobes in impulse control and planning, the involvement of the temporal lobes in adapting thoughts and actions to the environment, and the involvement of the posterior parietal lobes in identifying the individual's emotional context. Selective impairment in any of these areas could simulate certain as-

pects of such mental diseases as psychopathy, schizophrenia, and major affective disorder.

The clinician is faced with the seemingly insurmountable task of remaining familiar (or at least conversant) with rapidly accumulating data from distinct, remote, and often highly specialized areas of psychiatry. *Cerebral Hemisphere Function in Depression* gives clinicians the most concise, recent and in-depth analysis of research in this area available in a single source. The volume is divided into eight chapters, each highlighting and reviewing a specific area of importance.

Particularly well written are the chapters dedicated to the major cortical regions involved in affective disorders (chapter 4) and the patterns of structural cortical damage that generate behavior simulating depression (chapters 1 and 3). These chapters should be required reading for all psychiatrists interested in further understanding the physiological changes in the brain states associated with affective changes in normal individuals. Each chapter is well written and neatly edited in an enjoyable and understanding style. Graphs, tables, and diagrams are well chosen to highlight important material.

The final three chapters of this volume discuss methodological complexities that hamper the interpretation of information and research in this complex field. The real highlight of these chapters is the authors' creative construction of a future research model. They are able to rework current concepts into a new model designed to re-understand and more closely approximate evolving data. This is the real beauty and potential of basic and clinical research. Dr. Kinsbourne, the editor, is to be commended for attempting in his chapter to consolidate broadly divergent areas of research into a plausible and conceivable new model.

I highly recommend *Cerebral Hemisphere Function in Depression* to anyone interested in current research in affective disorder. This volume justifies its lofty goal of clarifying "the functioning of brain areas and neurotransmitters as interacting systems that generate change in mental states and react to changed mental states" (p. xiv). The book is a welcome and timely addition to the important Progress in Psychiatry series.

JOSEPH R. BONA, M.D.
Durham, N.C.

The Measurement of Depression: Clinical, Biological, Psychological, and Psychosocial Perspectives, edited by Anthony J. Marsella, Robert M.A. Hirschfeld, and Martin M. Katz. New York, Guilford Press, 1987, 411 pp., \$45.00.

Although it's probably inadvisable to burn on sight every book derived from a conference, the experienced reader of such volumes will do well to keep a Zippo handy. Self-aggrandizing content, clashing styles, thematic chaos, heedless duplications, and nonexistent editing all too often lurk behind an alluring title. Hence the reflex shudder upon finding that the present text is based on "papers at a workshop." Will it, too, live down to expectations?

The editors intend this book to "provide researchers, professionals, and students with a comprehensive and scholarly resource for identifying, understanding, and evaluating the many measures of depression presently in use." The 13 chapters represent "revised and updated" versions of discussion papers presented at a 1984 NIMH workshop in Honolulu and are categorized under Clinical Measurement, Biological Measurement, Behavioral and Psychological Measurement, and Psychosocial Measurement.

The book has some general problems. It is unclear whether

he intent is to describe measures of depressive symptoms, depressive syndromes, or depressive disorders; the absence of any detailed discussion of measures of suicidal thoughts, risk, or attempts seems curious in a "comprehensive" text. Then, too, the claim of "updated" chapters is dubious. For instance, the chapter on measuring neurotransmitters in depression—surely an area with rapidly accumulating research—cites only two references out of 140 that are more recent than 1983.

As a further shortcoming, some of the chapter authors have missed the stated point of the book and the editors don't seem to have noticed. Instead of focusing on "understanding and evaluating" the instruments and techniques, they give lengthy discourses on the results. Koslow and Gast's chapter on neurotransmitters and Stokes's chapter on neuroendocrine measurement are examples, as is Katz's chapter on the "multivantaged approach," which takes an inordinate amount of space to make the point that it is best to measure constructs in several different ways. Klerman's two introductory chapters on the nature of depression and organic depressive syndromes are not so informative as one might have hoped and contain a number of inaccuracies—including the repeated typographical error of "DMS-III." Marsella's concluding chapter on cross-cultural measurement buries a few good points in repetitious generalities, confusing figures, unexplained jargon, and inaccurate definitions (for example, "biopsychosocial" is defined as "cells, chemistry, organs").

A few chapters shine by contrast. Rabkin and Klein, after a slightly stilted introduction, provide sharp commentary on the common clinical scales for measuring depression. Andreasen gives a clear, straightforward overview of descriptive-level genetic measures. Rush's discussion of cognitive measures is a comprehensive yet concise account of the pros and cons of available instruments. John and Weissman deliver another in Weissman's series of lucid reviews of scales measuring social variables. The chapters on various psychological aspects of depression (one by Rehm, Lewinsohn, and Rohde and one by Hirschfeld and Cross) have useful information but with too much duplication.

As for physical aspects, the book has a sturdy binding, pleasing print, and an adequate layout. Typographical errors are too frequent, the index is fair to middling, and the price is too high for the value received. On balance, the book is not worth a space on your office shelf; look up the good chapters in the library's copy if you need them.

J. DEVANCE HAMILTON, M.D.
Houston, Tex.

SCHIZOPHRENIA

Search for the Causes of Schizophrenia, edited by E. Häfner, W.F. Gattaz, and W. Janzarik. New York, Springer-Verlag, 1987, 376 pp., \$78.00.

This multiauthored book is the result of a symposium of the same name held at Heidelberg in September 1986 to commemorate the 600th anniversary of the University of Heidelberg, the home of Emil Kraepelin, Karl Jaspers, and Kurt Schneider. The presence of these three giants in the field of schizophrenia is felt throughout the book and is highlighted by Dr. Zubin's closing comments. His penultimate chapter is must reading. It encompasses the history of progress in the understanding of schizophrenia by allowing Krae-

pelin, Jaspers, and Schneider to be reincarnated for one brief, insightful moment each (thanks to Dr. Zubin's fertile imagination and extraordinary ability to integrate knowledge historically and across disciplines) and to comment on the book's contributions. Examples from this chapter will give readers a flavor:

Emil Kraepelin: "I am somewhat perplexed by the extreme rigor you have applied [to diagnosis] . . . I am afraid this rigor may lead to rigor mortis for schizophrenia." "In the U.S.A. I once heard someone say, 'It ain't ignorance that causes all the trouble. It's knowing things that ain't so.' Perhaps we had to unlearn false knowledge before we could advance to the new."

Karl Jaspers: "They [the PSE, the SADS, and the other diagnostic instruments] can hardly reveal the rich phenomenology which patients experience."

Kurt Schneider: "The attempt on the part of *DSM-III* to classify the personality disorders through Axis II is a step in the right direction, since when an episode descends on an individual, he is already in possession of a primary personality which may color the nature of the episode."

Dr. Zubin clearly takes the opportunity to underline some of his own views and, in interviewing the three giants of schizophrenia, to outline for them the Zubin vulnerability model, which, on the whole, is the presumptive model of schizophrenia that ties all these assorted chapters together.

As Dr. Zubin explains, "According to the medical model, a person diagnosed as suffering with schizophrenia is essentially a sick person who, for longer or shorter periods, may appear to be well [in remission]." According to the vulnerability model, the person is essentially well and would remain so were it not for the exigencies of living, which elicit the vulnerability, producing longer or shorter episodes of illness.

In other words, the single locus gene (the hunt for which much of the book is indirectly about) is conceptualized not as pathogenic per se but as a variant of normal, a variant that under some as yet unspecified conditions uncovers a weakness, a failure in coping which leads to the different clusters and durations of schizophrenic symptoms. There are some interesting discussions in the book, notably by Drs. Häfner, McGuffin et al., and Baron about how ubiquitous the unspecified conditions need to be in order to fit the epidemiological and family data and how successful current classification systems are in designating an entity for which a gene can one day be found. Putative gene products as potential vulnerability markers are commented on by psychologists and biologists. Dr. Crow attempts to integrate many of the relatively undisputed facts (genetic transmission, seasonality of birth, primary involvement of the left hemisphere, genetic overlap with affective psychosis, and theoretically required but clinically missing evolutionary advantage) into a fanciful retro virus/transposon hypothesis. Dr. B.P. Dohrenwend et al. contribute a fascinating chapter on the life events issue (searching to specify the unspecified conditions). They come to the unexpected conclusion that life events (at least recent ones) are not important risk factors for episodes of schizophrenia. Dr. Angermeyer's chapter is among the most satisfying in that he approaches his subject, "Theoretical Implications of Psychosocial Intervention Studies on Schizophrenia," from the perspective of an experienced clinician interested in the welfare of individual patients and not at all—as many of the other authors do—from the viewpoint of the theoreticians who discuss individuals in terms of "cases" or points along a bell curve.

Much knowledge can be gained from this up-to-date book

on recent advances in schizophrenia. The authors have prepared comprehensive reviews, and Dr. Zubin has contributed a unifying theme. The concept of vulnerability is an attractive one, not only for students and budding scientists but also for practicing clinicians who are aware of the vulnerabilities of those they try to help and who struggle to find theories that apply to patients and not only to subjects, probands, cases, numbers, and dots along a line.

MARY V. SEEMAN, M.D.
PHILIP SEEMAN, M.D.
Toronto, Ont., Canada

Schizophrenia: Recent Biosocial Developments, edited by Costas N. Stefanis, M.D., and Andreas D. Rabavilas, M.D. New York, Human Sciences Press, 1988, 279 pp., \$36.95.

The symposium on Schizophrenia: Recent Biosocial Developments sponsored in 1984 by the Department of Psychiatry of Athens University has produced this small set of papers describing a variety of perspectives on the treatment of and research in the schizophrenic disorders. The papers cover a wide range of topics; the result is a volume offering something for everyone. Part one, Genetic, Biochemical, and Immunological Factors, starts with a chapter by Norman Sartorius that provides an excellent overview of the contributions made in schizophrenia research by the World Health Organization. Although veteran researchers will have absorbed this material elsewhere, newcomers to the field will find this very readable chapter informative. Dr. Sartorius's historical contribution is nicely complemented by a review of recent work from the Danish high-risk studies conducted by Fini Schulzinger and colleagues and a chapter by Timothy Crow discussing the possible role of viruses in schizophrenia. These chapters present readable and concise discussions of results that have emerged from these two research programs. The remainder of part one consists of two short research papers discussing results from immunological and neuroendocrine studies of schizophrenia.

In part two, Psychopathological, Psychophysiological, and Cognitive Factors, the opening chapter provides a discussion by Carlo Perris of the European concept of cycloid psychoses and their relationship to schizoaffective disorder. Dr. Perris provides some historical background that will be useful, especially to non-European researchers and clinicians. He also presents data supporting his hypothesis that cycloid psychoses are distinct from schizoaffective disorder. The remaining three chapters of part two discuss specific research studies and/or clinical observations of schizophrenic language, cognitive functioning, and electrodermal responses.

Unlike the first half of the book, part three, Treatment Issues, begins with a specific research study; this is followed by a broader review paper. Although the order of presentation in part three is somewhat distracting, it does not detract from the quality of the individual papers. In a review paper, John M. Davis and colleagues present some historical background on the psychological effects of antipsychotic drugs along with a concise review of their own work. This well-written chapter has the unusual quality of being appealing to both clinicians and researchers alike. In the opening research article, Yrjö O. Alanen and colleagues discuss a 5-year follow-up study of a psychotherapy program for schizophrenia. Although, as the authors note, this was not a research project in the strict sense (e.g., it did not have an adequate control group), the chapter does provide a comprehensive descrip-

tion of psychotherapeutic activities and their possible relationship to change and improvement in schizophrenia. The two closing chapters of part three are short research reports examining the effectiveness of naloxone for schizophrenic hallucinations and the effects of ECT on prolactin secretion among schizophrenic patients.

The chapters in the final section, Psychosocial Factors and Mental Health Services, may be especially appealing to those unfamiliar with European responses to deinstitutionalization and cost-effectiveness issues. Within this section there is a small gem of a chapter by John K. Wing discussing the problems of coping with schizophrenia in the home. This brief introduction to the reciprocal effects between the schizophrenic patient and family members is a must for those not familiar with Dr. Wing's work in this area.

It is unfortunate that the results of this 1984 conference could not have been published earlier. Given the pace of schizophrenia research, what was recent in 1984 has become history by 1989; therefore, this volume is unlikely to be of use to those who have kept abreast of the schizophrenia literature on a regular basis. On the other hand, many of the papers provide excellent and readable introductions to important areas of schizophrenia research or to specific programs of research that have made substantial contributions to the literature. These brief yet informative chapters would be most useful for medical students, residents, graduate students, or more experienced professionals who would like to update their schizophrenia knowledge base or sample some of the excellent work of our European colleagues.

STEPHEN V. FARAONE, PH.D.
MING T. TSUANG, M.D., PH.D., D.S.C.
Brockton, Mass.

Treating Chronically Mentally Ill Women, edited by Leona L. Bachrach, Ph.D., and Carol C. Nadelson, M.D. Washington, D.C., American Psychiatric Press, 1988, 184 pp., \$19.95.

We have come full circle: having spent the better part of the last two decades trying to demonstrate that many of the presumed behavioral differences between women and men have little empirical basis, we are now beginning to draw on such gender differences to call for the modification of the treatment of the chronically mentally ill. At the heart of the issue is whether male and female chronically mentally ill individuals differ enough to justify separate (or at least gender-tailored) treatment. Alternatively, does chronic mental illness overshadow such differences? Or, as suggested in this book by Bennett, Handel, and Pearsall, are the chronically mentally ill subject to attitudinal biases that prevent us from seeing them as sex-differentiated persons (p. 31).

The reader looking for simple, formulaic answers will not find this volume satisfactory. The participants in the Presidential Symposium at the 1986 annual meeting of APA, on which this edited book is based, take a critical, honest look at the specific problems encountered by chronically mentally ill women. Handel and Bennett, for example, document their conflicts of interest as administrators in deciding whether to implement a costly program for women knowing that such use of resources would deprive chronically mentally ill men.

Many questions demanding examination are raised. Why are gynecological examinations so often deferred among female psychiatric patients? What gender-related iatrogenic processes contribute to chronicity? How are the social, psy-

hological, and biological phenomena of pregnancy incorporated into treatment? The authors provide an invaluable service in bringing these types of problems to our attention and are to be commended for their thoughtful analysis. Ideally, these reports will spur others to more extensive and rigorous investigation.

It was especially heartening to find that some of the authors, such as Mary Seeman, are not afraid to examine biological differences and their implications for treatment. The inclusion of this perspective in the face of social pressure to underplay such processes is essential. With the exception of premenstrual syndrome, the study of female-specific biological processes (menarche, the menstrual cycle, pregnancy and birth, and menopause) and their relationship to psychopathology has generally fallen on hard times. (Male-specific biological processes, less easily demarcated, also deserve more attention.) Thus, we come to a point emphasized both implicitly and explicitly by the authors—that the treatment of chronically mentally ill women (and men as well) is a function of scientific, social, and political forces. If we are to further the care provided to the chronically ill of either sex, then we must clarify as best we can the appropriate boundaries for these various domains of inquiry. One hopes that the problems and ideas presented in this book will lead others to recognize the value of an orientation toward gender differences. Whether or not gender differences ultimately inform our understanding of the causes of psychopathology, our treatment of it will have been better for the effort.

RICHARD LEWINE, PH.D.
Atlanta, Ga.

SUBSTANCE ABUSE

Genetics and Alcoholism: Progress in Clinical and Biological Research, vol. 241, edited by H. Werner Goedde and Dharman P. Agarwal. New York, Alan R. Liss, 1987, 370 pp., \$60.00.

The controversy over the relative influences of nature and nurture in alcoholism continues to burn brightly. The title of this volume obviously places it in the "nature" camp, but the content periodically strays from a purely genetic approach. There are forays into metabolism, biochemistry, and neuropharmacology, the anticipated debate on heredity versus environment, and sections on completed and possible future research. The monograph represents the proceedings of an international conference conducted in Germany in 1986. There are 54 contributors representing 10 countries; 20 of the 54 are currently working in the United States.

The introductory section presents seven basic questions that serve to organize the volume: 1) Is alcoholism hereditary? 2) Are there genetically distinct forms of alcoholism? 3) What are the predisposing factors? 4) Is alcoholism a monogenic or polygenic disease? 5) Can genetic contributions be distinguished from environmental factors? 6) How are the biological risks transmitted? 7) Are there effective preventive measures that can modulate genetic influences?

The contributors proceed to address this ambitious but pertinent agenda in the chapters that follow. The aggregate quality of the writing is substantially better than usual in collections of this sort, and as most everyone familiar with alcoholism literature or the *Journal's* Book Forum has come to expect, Don Goodwin's brief chapter on adoption studies is masterful in the clarity and quality of its information, its

erudition, and a style that breezes us through otherwise bone-dry material. Nevertheless, a few chapters are difficult to follow as international authors come out on the losing end of a struggle with English syntax, punctuation, spelling, and idioms. Naturally, the responsibility for repairs rests with the editors, but their reluctance to help colleagues in distress is obviously based in the publication of manuscripts in the form of camera-ready copy. This copy is printed in almost as many typefaces as there are chapters, some are right-justified, some are not, and there is no consistency at all in the organization of references. This practice might be economically sound, but it is certainly not editorially responsible.

The case for an important genetic component to alcohol-related disease is well supported, and none of the authors has the poor sense to dogmatically insist that nature operates without a nurturing environment. Dr. Schuckit's chapter on populations at high risk is particularly useful, as is Dr. Martin's report of twin studies. The six chapters in the section on biochemical markers include some provocative glimpses of the future of diagnosis and treatment in alcoholism but probably will not give the working psychiatrist much that he or she will be able to use in the clinic next Monday morning.

The seven initial questions are all fairly satisfactorily dealt with by the time we finish the final chapter, but we might wish that the editors had stepped back for a postscript summarizing the variety of answers and drawing some ultimate conclusions. Alas, however, most of the opportunities for positive editorial influence in this book have been neglected, and most everything seems to have been too much trouble. Even the indexing, a once onerous task now vastly simplified by common computer programs, is poorly attended to. Such comparative irrelevancies as "Nazi Germany" and "novelty seeking," each mentioned only once in the text, are dutifully indexed, but antisocial behavior, a central consideration in alcoholism appearing on pages 24, 50, 53, 54, 63, 68, and probably elsewhere, is absent from the index. There is some good groundwork in this book, but the editors could have made it considerably better with a little effort. What we have here is the rough draft of a pretty good book.

WILLIAM E. FANN, M.D.
Houston, Tex.

Acid Dreams: The CIA, LSD, and the Sixties Rebellion, by Martin A. Lee and Bruce Shlain. New York, Grove Press, 1986, 343 pp., \$27.50; \$13.95 (paper).

Storming Heaven: LSD and the American Dream, by Jay Stevens. New York, Atlantic Monthly Press, 1987, 396 pp., \$19.95.

These two books re-open for analysis a chapter of American culture whose effects continue to influence us in many ways; that is, the use of hallucinogenic drugs in the United States in the 1950s to the 1970s. By so doing, they give us an opportunity to assess our own intellectual and emotional responses to these drugs, their use and abuse, their proponents and detractors, and the political climate associated with the abandonment of human research with them.

Many preliterate cultures, particularly in Latin America, Africa, and Asia, have a well-established tradition of using botanical sources of hallucinogens within a religious and/or magical context that both optimizes their effects and minimizes their adverse effects and abuse (1). However, once LSD (lysergic acid diethylamide) became widely available for un-

controlled self-experimentation in the United States, thousands of emergency room visits and psychiatric admissions occurred due to its unpredictable effects (2). Can drugs that have both undeniably mystical and/or religious ("psychedelic" or "mind-manifesting") as well as "psychotomimetic" effects ever be safely and rationally studied? These books, from slightly different perspectives, present the story of LSD (as the prototypical hallucinogen) and do not force any particular answers on us. Rather, they provide a wealth of historical, sociological, and political information with which we might understand the complex issues related to the human use of these compounds.

Lee and Shlain's work, a primarily political accounting of the role of LSD in the "1960s rebellion," partially relies on an exhaustive review of files (made available under the Freedom of Information Act) concerning the use of LSD by the CIA beginning in the early 1950s. The CIA, at the time, was working with several drugs for the purposes of national security. The authors also interviewed many of the individuals who were involved with LSD as a research, political, artistic, and psychotherapeutic catalyst or probe.

Briefly, soon after its discovery by Sandoz chemists in the 1940s, LSD was used by the CIA as one of several "truth drugs" for interrogation purposes. After the unpredictability of its effects was noted, its use as a debilitating compound was pursued. This work reached its most disturbing peak in "Operation Midnight Climax," in which a house of prostitution was established by the CIA in Greenwich Village and unsuspecting citizens were given LSD, then videotaped to determine its effects. The suicide of Dr. Frank Olson of the CIA, after he had been given LSD unwittingly in a drink (at a CIA weekend staff party, by a CIA psychiatrist), put an end to such "research." Many CIA-funded projects continued, however, primarily from the perspective of the "model psychosis" paradigm. According to this paradigm, the state induced by LSD could be used to model that of endogenous psychoses, giving psychiatrists a temporary direct experience comparable to that of their patients and/or providing insights into the biochemistry of severe mental illness. This approach developed in parallel with the psychotherapeutic work that exploited the "integrative experience" (a term developed by Sidney Cohen) that could be produced when LSD was given in an optimally supportive environment with proper preparation and follow-up. Such use was remarkably free of adverse effects (3).

Several chapters discuss the political and research background out of which LSD was introduced in the United States. Later chapters provide historical and political analyses of what happened when its use became much more widespread. Although Timothy Leary's publicity-oriented approach to hallucinogens is often blamed for the government's repression of hallucinogen research, many others were also part of a widespread movement that implicitly or explicitly encouraged self-experimentation. Ken Kesey, Alan Watts, Aldous Huxley, Henry Luce, Oscar Janiger, Allen Ginsberg, the Beatles, and the media phenomenon of the Haight-Ashbury district in San Francisco all contributed to what the interest of millions of Americans to try these drugs. The radicalization of American youth in the late 1960s and early 1970s and the tension that existed between the "psychedelic" and "political" factions (which continues to exist) are carefully detailed and analyzed. The final chapter is a cogent discussion of the present-day implications of millions of young Americans (now in their mid-30s to mid-40s) having taken these drugs.

Stevens's work is a more sociological and psychological

approach to the use of hallucinogens in the United States. Although much more detailed in its creation of a backdrop out of which particular phenomena emerged (e.g., the intellectual climate in Los Angeles surrounding Aldous Huxley Leary's personal history and dynamics, and the new role of psychology and psychiatry in creating an increasing powerful cultural ethos in the 1940s and 1950s), *Storming Heaven* is perhaps not so riveting or disturbing a work as *Acid Dreams*. This may be due to its personal rather than political perspective on the events of those times. However, the role of many more characters is fleshed out (perhaps we hear a bit too much about Dr. Leary), and the many conflicting drives, impulses, and wishes of individual and group and/or collective psyches are discussed in greater detail. Stevens clearly believes that much valid, valuable, and intriguing research was stopped in mid-stride by the passage of the drug abuse laws in the 1960s that made such work excessively difficult (i.e., the placement of all hallucinogens into Schedule I of the Controlled Substances Act). Ironically, the passage of these laws effectively ended all legitimate research but did nothing to stem the massive tide of street use and abuse that began at the same time. *Storming Heaven* concludes with a chapter discussing the apparently quite widespread use of the old and newer hallucinogens in the 1980s by individuals for both "therapeutic" and "recreational" purposes within a "neo-psychedelic" movement. Users are older, wiser, and more adept at managing crises. The use of such compounds, in Stevens's opinion, is continuing at an "underground" level.

These books, read together, provide a comprehensive and thought-provoking description and analysis of the events surrounding the introduction of hallucinogenic drugs into the United States. They clearly present the delicate and complex issues regarding some of the most interesting, maligned, and idealized compounds ever used by American psychiatry. The lack of clinical research into the mechanisms of action, therapeutic uses, prevention and treatment of adverse effects, and development of novel compounds in this fascinating family of drugs is a curious anomaly in our field. The historical perspective on the reasons for the abandonment of such research provided by *Acid Dreams* and *Storming Heaven* might encourage readers of these books to attempt such studies.

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RICK J. STRASSMAN, M.D.
Albuquerque, N. Mex.

EATING DISORDERS

The Role of Drug Treatments for Eating Disorders, edited by Paul E. Garfinkel, M.D., and David M. Garner. New York, Brunner/Mazel, 1987, 208 pp., \$22.50.

As the slender size of this volume suggests, at the current state of knowledge, drugs have a modest adjuvant role in the treatment of eating disorders. Each of the nine chapters addresses a particular class of drugs, from monoamine oxidase

inhibitors to neuroleptics. If the book in toto looks like a pharmacopoeia for psychiatric disorders, this impression is not by chance. Indeed, every psychotropic medication has been tried in anorexia nervosa, mostly with little success. The newer and better targeted drugs for bulimia nervosa have proven more promising and have been backed up by controlled studies. Hence, the book is an excellent practical guide to the currently available pharmacological treatment of bulimia nervosa.

Each chapter provides a description of the rationale underlying the use of a particular compound, reviews uncontrolled and controlled drug trials, and concludes with a recommendation. In several instances, for the neuroleptics, lithium, anticonvulsants, opioid antagonists, and drugs that facilitate gastric emptying, the counseled prudence and caution in their application is thoughtfully supported by the results of published material.

The difficult task of exploring the effectiveness of drugs for two similar yet dissimilar disorders, the aim in one of which is integration of weight gain and in the other is induction of satiety, is skillfully mastered by most contributors. In addition, not surprising in view of the fact that nearly half of the chapters are written by people connected with the editors, in-house work is sometimes too frequently quoted. One would have anticipated that Hilde Bruch's contribution, acknowledged only thrice, would have stayed alive a little longer.

In general, the chapters are well organized and carefully written and provide a truly up-to-date review of the pharmacology of eating disorders. In some instances where information about a drug's effectiveness is scant, there is a tendency to dwell excessively on theoretical principles and pathophysiology mechanisms, as in the section on gastrointestinal motility.

This book can be recommended to general psychiatrists, other medical specialists, and medical students who do not have the time to keep up with the contemporary literature as a useful and critical overview of drugs tested for the treatment of eating disorders.

REGINA C. CASPER, M.D.
Chicago, Ill.

Pathology of Eating: Psychology and Treatment, by Sara Gilbert, B.A., M.Sc. New York, Routledge & Kegan Paul and Methuen, 1986, 234 pp., \$35.00.

This book fills a place in the eating disorders literature that has long been vacant. It is an introductory book of modest length that covers anorexia, bulimia, and obesity from a relatively unbiased perspective. Ms. Gilbert brings together a diverse body of research and allows it to tell the story of eating disorders while only rarely revealing her own views. With 622 references (by my count) crammed into a short text the reader need not worry about being overburdened with an excess of material in any one area. Research from the fields of cognitive and behavioral psychology, family therapy, psychoanalysis, biological psychiatry, psychosomatic medicine, physiology, and nutrition are all included. Just about the only thing missing is specific diet programs. The outcome is a text that reads something like an extended, rapid-fire review of the literature.

The book is divided into three sections. There is an introductory section called Normal Eating Behaviour, which examines cultural influences and the control of eating behavior. The second section, Pathology of Eating, addresses defini-

tions, phenomenology, epidemiology, and etiology. The focus is on how each of these issues relates to eating behavior rather than to specific diagnoses. Thus, anorexia is discussed as an expression of restrictive eating behavior and obesity and bulimia are paired as expressions of excessive eating behavior. This explains the all-encompassing sound of the title and proves to be a welcome change from the more typical pairing of anorexia and bulimia and the separate consideration of obesity. It takes the reader away from the perspective of an observer of psychiatric syndromes and closer to that of an observer of human behavior. It also provides an integrative framework that other texts on eating disorders have been hard pressed to find. Ms. Gilbert makes clear, however, that her grouping of the disorders is not entirely correct. This is because all three disorders move back and forth between the categories of restrictive and excessive eating at different times in their courses. Ultimately all three disorders are linked by the preoccupation of the affected individuals with weight, dieting, and body image—commonalities that lead to a range of overlapping behaviors.

The final section, Treatment of the Eating Disorders, again follows the published research, this time going through each disorder in turn. Here Ms. Gilbert is concerned with what approaches have been shown to be effective. Behavioral therapies get the most discussion across all three disorders. Perhaps this is due to the proliferation of research in behavioral and cognitive treatments for eating disorders in the last 20 years. However, this does not explain the paucity of material presented on pharmacological treatment, on which there has also been considerable research. The pharmacotherapy discussions also tend to be unrepresentative of the current state of the art. Behavioral therapies are discussed both as treatments in their own right and for their role as adjuncts to other therapies as a means of improving compliance. The author is clearly at her best when discussing behavioral approaches to obesity. Here she allows her presentation to be led by her own reasoning, turning to applicable research only as needed. In much of the rest of the book the available research seems to take precedence and Ms. Gilbert's reasoning follows.

Because of this general preference to put the data first one sometimes gets the feeling of reading lots of disconnected bits of information—a style that makes it difficult to know just what to come away with at the end of a chapter. This is reinforced by the fact that the author does not supply summarizing comments at the close of each chapter and by the inadequacy of the subject index. As a result we have a book that is bursting with information, but the information is in a form that tends to pass through the reader before it has a chance to be absorbed and metabolized.

One overriding message does come through time and again from Ms. Gilbert's commentary and from the research she presents. That is the message of the intricate weaving of the psychological with the physiological and the cultural with the biological. Such distinctions are often impossible to make in this field, and when they are made they are often later found to be inaccurate. By pointing this out, Ms. Gilbert has brought eating disorders more solidly within the discipline of psychosomatic medicine. *Pathology of Eating* does a good job at introducing us to the complexities.

HENRY SCHWARTZ, M.D.
White Plains, N.Y.

The Etiology and Treatment of Bulimia Nervosa: A Biopsychosocial Perspective, by Craig Johnson and Mary E. Connors. New York, Basic Books, 1987, 352 pp., \$22.95.

In this outstanding book, Craig Johnson and Mary Connors describe the etiology and psychopathogenesis of bulimia nervosa in terms of the biopsychosocial model. The authors then present a comprehensive overview of assessment, treatment recommendations, and methods for managing the symptoms of binge eating and purging behavior.

In the first three chapters, the history, epidemiology, and demographic characteristics of bulimia are reviewed. Historically, bulimia was first associated with anorexia nervosa, then with obesity. Currently it is defined without reference to weight. In the chapter entitled "Epidemiology," an excellent review of the prevalence studies is provided; these indicate that only 1.3% of women binge eat and purge by self-induced vomiting. This figure is substantially lower than the ones frequently cited by the lay literature and is undoubtedly more accurate.

In the chapter entitled "Personality Profile," the personality characteristics of bulimic patients as reflected by various psychological tests such as the MMPI and Rorschach are reviewed. The lengthy chapter entitled "Developmental Considerations" is well worth reading. Current psychodynamic theories of the development of the self are briefly outlined and the developmental deficits that frequently occur among bulimia nervosa patients are presented. The section describing the consequences of maternal over- and underinvolvement in the development of character pathology is particularly useful in understanding the origin of certain bulimic symptoms. Within this chapter are several case reports that illustrate particularly well the theoretical framework pre-

sented. This chapter is probably the most useful for the experienced therapist working with bulimic patients.

In part two, the authors describe assessment and treatment. In the chapter "The Initial Interview" the authors state that each patient with bulimia is unique and that "packaged" treatment programs are probably not effective. This chapter includes the Diagnostic Survey for Eating Disorders, which is a questionnaire designed to elicit demographic and symptomatic data quickly. The chapter entitled "Treatment Recommendations" outlines possible treatment alternatives and their indications. At the end of this chapter there is a poignant reprinted story entitled "Helen Frank: Being Thin Is the Most Important Thing in My Life." I have asked several patients to read this story of an older woman whose life is an empty shell of obsessions about food; they have found it to be very thought provoking. The chapters "Techniques for Symptom Management" and "Special Treatment Issues" include detailed descriptions of various behavioral strategies and techniques useful in group and individual psychotherapy with bulimic patients. In view of the recent interest in psychopharmacological approaches to treatment of bulimia, the sections on the use of medication were probably too brief. The last chapter, "Review of Treatment Studies: Methodology and Efficacy," reviews the effectiveness of the various treatment modalities including psychological and pharmacological interventions.

In summary, this is an excellent book that provides a comprehensive overview of the etiology, assessment, and treatment of bulimia. The beginning therapist will find the assessment and treatment sections useful, and the experienced therapist will find the chapter on developmental considerations very helpful.

PAULINE S. POWERS, M.D.
Tampa, Fla.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Syndrome of Inappropriate Secretion of Antidiuretic Hormone Due to Fluoxetine

SIR: We have observed prolonged hyponatremia in a patient who was treated with fluoxetine for major depression. We believe that this was a case of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) induced by the heterocyclic antidepressant fluoxetine rather than by the patient's psychiatric illness. As far as we can determine, there has not been a report of SIADH as a possible side effect of fluoxetine.

For several years, Mr. A, a 75-year-old white male veteran, had had bouts of severe depression, which had been successfully treated with trazodone, up to 450 mg/day, until several months before his admission to the hospital with worsening symptoms of depression. He had severe insomnia, crying spells, and a pervasive lack of energy. Fluoxetine, 20 mg every morning by mouth, was started after discontinuation of the trazodone, and for the first time in several months, he had very satisfactory uninterrupted sleep on the second night after starting the fluoxetine.

Mr. A's serum sodium and chloride levels were within normal limits on admission. Lower than normal serum levels of sodium and chloride (130 and 95 mmol/liter, respectively) were first detected 10 days after he had begun taking fluoxetine; these levels gradually decreased further, reaching the nadir of 126 mmol/liter of sodium and 89 mmol/liter of chloride 4 days later. The next day, osmolality of serum and osmolality of urine were lower than normal: for serum, 264 mosmol/liter (normal range=276–305); for urine, 417 mosmol/kg (normal range=500–800), consistent with SIADH. Polydipsia had not been observed during this period. It was thought that fluoxetine was responsible for this condition, and so the fluoxetine was discontinued. Daily checks of serum electrolyte levels showed gradual return to normal levels by the 10th day after discontinuation of fluoxetine. The patient was subsequently started on trazodone again, which led to successful control of his depression. Serum electrolyte levels remained normal throughout the treatment with trazodone.

SIADH is known to occur in various medical and psychiatric conditions. The psychiatric conditions include schizophrenia (1), depression (2), and mania (3). It is also known to be produced by many pharmacological agents, including psychotropic drugs such as heterocyclic antidepressants and antipsychotics (4). As in this case, hyponatremia is known to develop without being preceded by polydipsia in SIADH stemming from either psychiatric illness or treatment with psychotropic medications (2). It is not known why a patient develops SIADH after treatment with one particular antidepressant but not with other similar agents. We decided not to carry out a challenge test with fluoxetine because of this

patient's advanced age. Although this case report provides only a tenuous argument for listing SIADH as a possible side effect of fluoxetine, the grave consequences that could have resulted from failure to discontinue the medication prompted us to report this case.

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ANDREW S. HWANG, M.D.
St. Paul, Minn.

RICHARD M. MAGRAW, M.D.
Minneapolis, Minn.

Extrapyramidal Symptoms in a Patient Taking Haloperidol and Fluoxetine

SIR: I should like to report the following case.

Ms. A, a 39-year-old woman with bipolar disorder, developed severe, intractable extrapyramidal symptoms while taking haloperidol and fluoxetine. She had been taking haloperidol, 2–5 mg/day, for 2 years, both with and without benztropine, and had experienced only occasional, mild extrapyramidal symptoms, which had always quickly remitted with reduction or discontinuation of the haloperidol. Haloperidol had been more effective than lithium, cyclic antidepressants, or monoamine oxidase inhibitors in providing relief from her severe, persistent depressions. Haloperidol alone was effective in preventing her manic episodes. Carbamazepine had not yet been tried in this patient. The haloperidol had been stopped 2 weeks before the onset of the severe extrapyramidal symptoms because of the presence of mild oral-buccal movement abnormalities.

Five days before the haloperidol was stopped, Ms. A had started taking fluoxetine, which was increased to 40 mg b.i.d. over several days. We hoped that this newly released antidepressant would prove more effective than the others we had tried. She was taking no other medications at this time.

After taking fluoxetine for 2 weeks, Ms. A took 5 mg of haloperidol on two consecutive mornings while continuing the fluoxetine. She then began to experience severe tongue stiffness, parkinsonism (*petits pas* gait, cogwheel rigidity,

flattened facies), and akathisia. The haloperidol and fluoxetine were discontinued.

She was hospitalized and started on a regimen of benzotropine, amantadine, diphenhydramine (oral and intravenous push), and diazepam, none of which produced marked improvement. Her haloperidol blood level at admission was less than 5 ng/ml (the sample was drawn 30 hours after she took the last 5 mg of haloperidol). Over the next 7 days the extrapyramidal symptoms slowly remitted, but for the first 3 days of hospitalization Ms. A was virtually incapacitated.

Seven days after admission the patient was restarted on antipsychotic medication, i.e., perphenazine (later switched to haloperidol, up to 30 mg/day, with benzotropine, 6 mg/day); a slight parkinsonian gait returned, but there were no other extrapyramidal symptoms.

This patient experienced severe extrapyramidal symptoms only while taking both haloperidol and fluoxetine; she was able to take haloperidol alone, before and after fluoxetine was added to her regimen, without developing these severe symptoms. It seems probable that the haloperidol-fluoxetine combination was responsible for the severe extrapyramidal symptoms. I have been unable to find any reported instances of such interaction.

JEFFREY L. TATE, M.D.
Houston, Tex.

Carbamazepine-Induced Mania With Hypersexuality in a 9-Year-Old Boy

SIR: Carbamazepine, a tricyclic compound derived from imipramine, is assuming an expanding role in the treatment of psychiatric conditions. Its usefulness has been reported in affective and behavioral disorders, episodic dyscontrol, and psychosis (1). Studies have suggested that tricyclic antidepressants can precipitate mania. However, a literature search revealed only four cases of carbamazepine-induced mania in children and adolescents (2, 3). We wish to report the case of a 9-year-old boy who developed a manic episode following the administration of carbamazepine. To our knowledge, this is the youngest patient reported to have developed carbamazepine-induced mania. Furthermore, although hypersexuality is common in adolescents with mania (4), we believe this is the first report of hypersexuality occurring in a prepubertal manic patient.

Alex, a 9-year-old black boy, was admitted to a children's psychiatric unit for depression associated with suicidal feelings, pervasive physical aggressiveness, uncontrollable behavior, and stealing. There was a history of maternal physical abuse and neglect, and sexual abuse was suspected. The family psychiatric history revealed only cocaine dependence in the mother. Physical examination showed an undernourished, prepubertal black child with numerous well-healed scars. Laboratory studies revealed iron-deficiency anemia and *Ascaris lumbricoides* infestation. An EEG was normal. The initial diagnoses were major depression and conduct disorder.

Alex's suicidal feelings remitted and his depressive symptoms lessened shortly after hospitalization. His aggressiveness, which included striking and biting staff members and patients, responded partially to behavioral modification and thioridazine, 100 mg/day. Refractory ag-

gressive outbursts, which averaged three times a week, were treated with carbamazepine, 100 mg b.i.d. A steady serum level of 4.2 µg/ml was achieved. After 10 days without improvement, the carbamazepine was increased to 100 mg t.i.d. Within 48 hours a marked deterioration in Alex's behavior occurred. Symptoms included loud and pressured speech, frequent assaultive and destructive behavior, irritability, expansiveness, decreased need for sleep, motor hyperactivity, and hypersexuality. He removed his clothes and masturbated openly while making obscene gestures and solicitations. Overt sexual activity was directed indiscriminately toward male and female peers and the staff. His carbamazepine level at this time was 5.2 µg/ml. During this episode he did not exhibit signs of neurological toxicity such as disorientation, ataxia, or slurred speech. No hallucinations, incoherence, or loosening of associations was present to suggest acute psychosis. The boy returned to baseline functioning 4 days after the carbamazepine was discontinued.

This patient met the *DSM-III-R* criteria for manic episode. The existence of mania as a diagnostic entity in children is accepted as rare but valid. While neurotoxicity occurring with the combination of carbamazepine and neuroleptics has been reported (5), the patient demonstrated no evidence of this.

Adverse behavioral effects infrequently associated with the use of carbamazepine include talkativeness, irritability, insomnia, and agitation (1). It seems reasonable to suspect that these side effects may at times be unrecognized episodes of mania or hypomania. This report provides additional evidence for carbamazepine's role in the precipitation of mania. Furthermore, this case alerts clinicians that hypersexual behavior in prepubertal children may signal mania.

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WADE C. MYERS, M.D.
FRANK CARRERA III, M.D.
Gainesville, Fla.

Seizure Disorder Misdiagnosed as Borderline Syndrome

SIR: There is growing concern that the diagnosis of the borderline syndrome is not infrequently made capriciously and subjectively and that it may be used as an easy escape for labeling untreatable patients (1-3). Labeling of this type can inhibit the search for, and identification of, other psychopathogenic processes, for which effective therapies are available. The following case history illustrates how, in a patient who had a diagnosis of borderline syndrome, the basic problem was an unrecognized atypical seizure disorder.

Ms. A, a 51-year-old former professional woman, was admitted to the hospital with diagnoses of 1) depression, major, recurrent, and 2) personality disorder, borderline, after one of many suicide attempts involving an overdose of clonazepam and aspirin. During the preceding 15 years she had had numerous admissions to other psychiatric hospitals, during which she had been treated with antidepressants, neuroleptics, extensive psychotherapy, and several courses of ECT—all with only minimal success. Her confusion and memory/concentration difficulties in the period immediately after the overdose were attributed to residual effects of the drugs she had taken. However, psychological testing 1 month later showed extensive and severe cognitive and memory deficits.

Most intriguing were Ms. A's reports of episodic "attacks" consisting of impairments of consciousness and subsequent difficulties with memory and concentration. Her suicide attempts appeared to be related to periods when she was experiencing extreme confusion and disorientation; she had subsequent amnesia for the acts themselves. These reports were supported by observations, made during the current hospitalization, of brief episodes of myoclonus involving upper and lower extremities, "staring into space," and nonresponsiveness to verbal commands that lasted up to 6 minutes. During these episodes, consciousness was not lost and there was no incontinence, no vocalization, and no falling down or tongue biting.

Subsequent studies revealed the following information. Routine EEGs were normal. Magnetic resonance imaging studies of the brain showed no abnormalities. A brain scan indicated possible low-density areas involving the right visual cortex and basal ganglia. A brain electrical activity mapping (BEAM) study showed extensive abnormalities in the mid-central, mid-parietal, right frontal, and left mid-temporal regions on visual evoked-potential testing. Auditory evoked-potential testing revealed highly significant asymmetric activity in the left occipital and the right and mid-central regions.

With daily doses of 800–1000 mg of carbamazepine, Ms. A became entirely free of episodes of myoclonus, confusion, disorientation, amnesia, and suicidal behavior.

The cause of this patient's seizure disorder and BEAM findings remains obscure. A history of head injury during adolescence and a concussion suffered in 1984 are possible factors, as is her exposure to multiple courses of ECT (4).

This case illustrates the value of periodic scrutiny and re-evaluation of psychiatric diagnoses, especially since newer diagnostic procedures such as BEAM make possible the recognition of hitherto undiagnosable disorders. This policy is especially important with patients who have the diagnosis of borderline syndrome, in view of the apparent frequency with which this disorder is incorrectly diagnosed by default.

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ELIZABETH M. SCHMID, M.D.
MARSHALL J. HANDLEMAN, M.D.
T. GEORGE BIDDER, M.D.
Los Angeles, Calif.

What To Do About Extremely High Plasma Levels of Tricyclics?

SIR: The increased availability of methods for determining plasma levels of tricyclic antidepressants has been of value in permitting clinicians to maximize clinical response. In general, above a certain plasma level (or dosage), toxic effects will begin to emerge that outweigh the beneficial response to the antidepressant (1). Occasionally, there are patients without notable ill effects whose plasma levels of tricyclics are dangerously close to toxic levels despite their taking only therapeutic doses. We recently treated one such patient in a case that highlighted this paradox of psychopharmacologic practice.

Ms. A, a 24-year-old woman admitted to a long-term inpatient unit, presented with suicidal ideation, disturbed sleep, and social withdrawal. Desipramine was initiated at 25 mg/day and was gradually increased to 250 mg/day without problems in compliance. She received no other psychopharmacologic medication nor did she take nonpsychopharmacologic agents that could increase plasma levels of desipramine, co-chromatograph with it, or otherwise affect tricyclic metabolism. Her normal sedimentation rate ruled out an acute inflammatory process, which could elevate tricyclic plasma levels because of increased levels of α_1 acid glycoprotein. The depressive symptoms cleared, and the patient suffered no obvious ill effects. ECGs, which included measurement of the P-R interval, were within normal limits.

Ms. A's desipramine level, from a sample drawn 12 hours after the last dose (4 days after the 250-mg dose began) and remeasured from the same sample, was 867 ng/ml (3.5 ng/ml per milligram). According to the National Psychopharmacology Laboratory, Inc., this is almost three times the normal maximum of 300 ng/ml. Furthermore, this result was probably an underestimate of what the steady-state level would have been if 7–10 days at the maximum dose had elapsed before the assay was performed (1). Lowering the dose of desipramine to 150 mg/day produced a reading of 679 ng/ml (4.5 ng/ml per milligram). Two weeks after the desipramine was further reduced to 75 mg/day, a steady-state plasma level of 330 ng/ml (4.4 ng/ml per milligram) was noted. (The antidepressant's linear pharmacokinetics, confirmed by these data, imply that clinicians need not routinely make multiple determinations of tricyclic plasma levels. At 75 mg/day of desipramine, however, Ms. A had a recurrence of depressive symptoms despite the addition of lithium carbonate for antidepressant augmentation.)

Garvey et al. (2) noted that two patients taking imipramine required elevated plasma levels of the drug for improvement. Another group (3) reported a similar case involving desipramine. There are, however, no long-term systematic follow-up studies on these patients to indicate whether they

are at risk for such untoward events as sudden death. Furthermore, unrelated to the treatment, the recording of such an elevated plasma level in the patient's chart could leave the practitioner liable if adverse physical or behavioral manifestations should arise later. These sobering considerations must be balanced against the possibility that the patient may relapse and not respond to either lower doses of the tricyclic or alternative therapy. Could a patient experiencing such a treatment failure request, with proper informed consent, to return to the *offending* drug at its previous dosage?

We ultimately chose not to enter a psychopharmacologic no man's land before exhausting the approaches available in an inpatient setting that specializes in comprehensive long-term care. On the other hand, practitioners who do not have ready access to this kind of resource will need to decide, with proper consultation, the amount of prolonged uncertainty they are willing to accept. There is a clear need for research examining such issues as 1) which patients develop high plasma levels of tricyclic antidepressants, 2) what the long-term risk in these patients is, and 3) how we can reliably identify patients who need high levels and do not get into difficulties. We hope that these reflections will spur investigations that expand treatment frontiers rather than narrowing further the Procrustean bed of defensive medicine.

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DAVID L. GOLDMAN, M.D.

STEPHEN E. KATZ, M.D.

Topeka, Kan.

SHELDON H. PRESKORN, M.D.

Wichita, Kan.

Pharmacological Dissection of Panic and Depersonalization

SIR: Depersonalization disorder is classified as a dissociative disorder in *DSM-III-R*. The essential feature is the occurrence of persistent or recurrent episodes of depersonalization sufficiently severe to cause marked distress. The diagnosis is not made when the symptom of depersonalization is secondary to any other disorder, such as panic disorder or agoraphobia without history of panic disorder.

We recently treated a patient with panic disorder who also had depersonalization symptoms of sufficient severity to meet the criteria for depersonalization disorder. However, in the presence of a panic disorder, this diagnosis was hierarchically excluded.

Ms. A, a 17-year-old female high school student, had a 3-year history of chronic depersonalization symptoms occurring several times a day: "everything feels unreal, things seem out of place and too close, there is a foginess like a veil is over everything, I feel nauseated, and I feel separate from my friends." In addition to this condition, two or three times a week the patient experienced intermittent panic attacks that came on suddenly and lasted

10-15 minutes, with palpitations, fear of going crazy sweating, hot and cold flashes, shaking, and severe anxiety

Two months of insight-oriented psychotherapy on a weekly basis had produced no benefit. Two years after the onset of symptoms, Ms. A was started on a regimen of imipramine, 10 mg/day, which was gradually increased to 340 mg/day over a 6-month period. This resulted in a complete resolution of the panic attacks, but the depersonalization symptoms were unchanged.

With the recurrence of partial breakthrough panic attacks, alprazolam, 1.0 mg/day in divided doses, was added. Again, the panic attacks were completely blocked but the depersonalization disorder remained unchanged. After 6 months, the imipramine and alprazolam were tapered slowly and discontinued, and fluoxetine, 10 mg/day, was added. The fluoxetine was gradually increased to 60 mg/day over a 6-week period. By the 11th week after starting fluoxetine, Ms. A had a marked reduction in depersonalization symptoms and the panic remained in remission. The depersonalization episodes, which had previously occurred several times a day, were reduced to only a few times a week. Ms. A continued to improve during an additional 2 months of follow-up.

Sir Martin Roth described a "phobic anxiety depersonalization" syndrome which lumped panic and depersonalization together (1), and *DSM-III* followed this in establishing a hierarchy. Previous studies of pharmacological dissection have supported the distinction of panic disorder, agoraphobia, and generalized anxiety disorder (2). In addition, distinctions between panic and depression have been supported (3). This report suggests that panic and depersonalization symptoms may respond selectively to pharmacological agents, even when both kinds of symptoms are present in the same patient. In this case the panic symptoms resolved with imipramine and alprazolam, whereas the depersonalization symptoms were unaffected. However, the depersonalization symptoms responded to fluoxetine, a selective serotonin reuptake blocker, and the panic symptoms did so as well. This suggests differences and similarities in the pathophysiology of panic and depersonalization and calls into question the statement in *DSM-III-R* that the diagnosis of depersonalization disorder is not made when panic is present. Studies of comorbidity suggest it is conceivable that panic is a lesser form of depersonalization (4), and serotonin reuptake blockers might be an effective treatment.

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ERIC HOLLANDER, M.D.

JANET FAIRBANKS, M.D.

CONCETTA DECARIA, M.D.

MICHAEL R. LIEBOWITZ, M.D.

New York, N.Y.

Bromocriptine Treatment of Cocaine Withdrawal Symptoms

SIR: *DSM-III-R* recognizes cocaine dependence as a diagnosis. Because cocaine withdrawal symptoms—drug craving, depression, low energy—can cause treatment dropout and recidivism, a specific treatment for cocaine withdrawal would be useful. The role of dopamine in cocaine euphoria and the dopamine depletion hypothesis of cocaine withdrawal led to a placebo-controlled, single-blind study which showed that a single dose (0.625 mg p.o.) of the dopamine agonist bromocriptine reduced the cocaine craving associated with cocaine abstinence and had minimal side effects (1). Another study found amantadine and bromocriptine (up to 2.5 mg t.i.d.) effective in alleviating the symptoms of cocaine withdrawal, although bromocriptine produced substantial side effects (2).

To study the utility of bromocriptine in cocaine withdrawal in a clinical setting, we administered bromocriptine in an open study to 10 consecutive male patients (20–35 years of age) hospitalized for crack cocaine dependence who manifested considerable withdrawal symptoms. They gave written informed consent for bromocriptine treatment. Patients undergoing alcohol, sedative, or opioid withdrawal were excluded. The doses of bromocriptine and duration of the treatment were based on clinical response and ranged from 0.625 to 1.875 mg t.i.d. orally for 6–20 days. Patients rated their cocaine craving, energy, and mood on 100-mm-line rating scales.

Mean \pm SD ratings improved significantly over baseline by the second day of bromocriptine treatment: craving decreased from 47 ± 25 to 11 ± 8 ($t=4.65$, $df=8$, $p<0.01$, two-tailed test), energy increased from 32 ± 19 to 61 ± 22 ($t=-2.59$, $df=7$, $p<0.05$), and depression decreased from 50 ± 25 to 26 ± 20 ($t=3.05$, $df=7$, $p<0.05$). A retrospective chart review in which the Clinical Global Impression scale was used showed a mean \pm SD score of 1.9 ± 0.6 (much improved) by the second day. Bromocriptine's reversal of cocaine withdrawal distress was sustained for the duration of treatment, with little recurrence of distress after discontinuation of the bromocriptine. Except for mild nausea in several patients, no significant side effects were noted. All 10 patients completed the inpatient addiction treatment program and were no longer taking bromocriptine at discharge. There was no evidence of a euphoric effect from bromocriptine, nor did the patients show any inclination to continue the medication past the time recommended.

This preliminary open trial suggests a role for bromocriptine in detoxifying hospitalized patients dependent on cocaine and in facilitating other aspects of the treatment program. A recent pilot study of methadone patients supported the efficacy of bromocriptine (2.5 mg/day) in reducing cocaine use and craving (3). The efficacy of bromocriptine in cocaine withdrawal supports the dopamine depletion hypothesis of cocaine dependence, as do the report of decreased cortical dopamine in rats administered cocaine (4) and a preliminary study by our group that showed decreased plasma levels of the dopamine metabolite homovanillic acid in cocaine addicts who were being detoxified. The efficacy of bromocriptine is not inconsistent with reports that noradrenergic tricyclics such as desipramine improve outcome in the treatment of cocaine dependence (5), although a preliminary study by our group suggested that bromocriptine may be more efficacious than desipramine in acute cocaine withdrawal.

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IRL L. EXTEIN, M.D.
DAVID A. GROSS, M.D.
MARK S. GOLD, M.D.
Delray Beach, Fla.

Longitudinal Assessment of Older Schizophrenic Patients

SIR: Longitudinal evaluation of chronic mental patients provides insights into the clinical course of acute and chronic extrapyramidal syndromes, which cross-sectional appraisal does not. Follow-up rates of younger cohorts (mean ages = 28–52 years) typically range from 50% to 75% (1, 2). There is less longitudinal information about older patients with schizophrenia despite the greater vulnerability of this population to extrapyramidal symptoms. Thus, we were unsure how many older patients would be available for our follow-up study. We recently completed a 2- to 4-year reevaluation of 31 older chronic schizophrenic patients who had been initially assessed for extrapyramidal symptoms, ventricular size, and cognitive deficits (3).

The original group was composed of 31 patients (mean age = 65 years, range = 55–75 years) who met the *DSM-III* criteria for schizophrenia and had been treated with neuroleptics for at least 10 years. All were patients at the VA Medical Center in Portland, Ore., and had agreed to be reexamined at a later time. No specific attempt was made to maintain contact with the patients during the interval before follow-up. Most patients were located for reexamination by searching the Portland VA Medical Center patient data base to identify those still in treatment. Location of a few patients who had left the area required considerable effort and some detective work on our part. All available charts were reviewed for last known address, records of commitment to state facilities, next of kin, and any administrative actions that provided clues to a patient's whereabouts. Two veterans who received pensions were located through the VA regional office.

Twenty-three (74%) of the original 31 patients were reexamined. Of these, 20 still resided in the Portland area and were being followed at the VA outpatient clinic. Two others lived close enough to travel to Portland for evaluation, and a third was examined when he was admitted to the hospital for exacerbation of psychosis. We accounted for seven of the eight patients not reevaluated; three had died and four had moved out of the area (two of them to Florida). All of the patients who had moved indicated that they would have participated in the follow-up had they lived nearby. The whereabouts of the last patient remain unknown.

We were able to reevaluate a substantial proportion of

these older patients. Studies of younger groups of chronic schizophrenic patients often include high percentages of patients lost to follow-up and patients who refuse reevaluation. The availability of this older group for longitudinal study differed substantially from that of younger patients. None of the subjects refused reexamination, and only one was completely lost to follow-up. Older schizophrenic patients represent an understudied segment of the chronically mentally ill; because of their relatively low mobility, they are well suited to short-term longitudinal studies.

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WILLIAM F. HOFFMAN, PH.D., M.D.
LINDA C. BALLARD, R.N., M.S.
DANIEL E. CASEY, M.D.
Portland, Ore.

Lithium and Carbamazepine-Induced Agranulocytosis

SIR: Dominique Servant, M.D., and colleagues (1) reported a case in which they suggested that lithium carbonate reversed the agranulocytosis which occurred secondary to carbamazepine treatment. Although this is one possible explanation for the authors' clinical observations, we would like to raise several caveats about their conclusions.

First, they failed to distinguish between the different hematological effects that occur with carbamazepine treatment. Substantial but limited decreases in leukocyte counts (benign leukopenia) are frequently associated with carbamazepine treatment (2, 3). These decrements in hematological indexes are distinct from the rare idiosyncratic cases of agranulocytosis and aplastic anemia that are estimated to occur in approximately six and two cases, respectively, per million patients exposed, or 1/125,000 (3).

Second, it has been observed (4, and Kramlinger and Post, unpublished observations, 1988) that lithium treatment counteracts these benign carbamazepine-induced leukopenias. In all these instances, the addition of lithium to carbamazepine treatment reversed the reductions in total white cells (4) by selectively increasing neutrophil counts but not lymphocytes. In addition to granulocytic stimulation, lithium increases platelet counts by activating colony-stimulating factors for granulocytes and platelets but not for red cells (5).

Third, in the case report of Dr. Servant and associates, lithium treatment was begun 21 days before the onset of rash and leukopenia, concomitant with carbamazepine, and extended throughout the reduction and recovery of WBC indexes. Therefore, not only is it uncertain whether the lithium had a therapeutic effect in this patient, but the opposite might be argued, i.e., that lithium failed to prevent the serious type of idiosyncratic agranulocytic reaction induced by carbamazepine. The WBC count recovery following discontinuation of carbamazepine may have been spontaneous and, as has been previously reported, unrelated to lithium. Even if recovery were facilitated by lithium, it is ominous that the agranulocytosis developed in spite of lithium cotreatment.

Last, it is of interest that the patient reported by Dr. Servant and colleagues had developed both an allergic skin eruption and a clinically significant granulocytopenia. While this may suggest a common allergic etiology, it is our clinical experience that these two complications of carbamazepine treatment do not invariably occur together. Ten percent to 15% of our patients have developed a skin rash when taking carbamazepine, while maintaining normal hematological indexes. On the other hand, patients who have developed leukopenia have done so without any skin complications. Therefore, the coexistence of these two conditions does not necessarily indicate the mechanism of the agranulocytosis.

We would be cautious in suggesting that lithium may reverse severe, potentially fatal cases of carbamazepine-induced agranulocytosis, although it clearly does reverse the benign granulocytopenia syndrome (4). Instead, the data presented by Dr. Servant and associates may represent the first evidence that lithium is unable to prevent the development of the rare, idiosyncratic carbamazepine-induced agranulocytosis.

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RUSSELL T. JOFFE, M.D.
Toronto, Ont., Canada
ROBERT M. POST, M.D.
Bethesda, Md.

Importance of the Transference and Therapeutic Alliance in Pharmacotherapy

SIR: Although Irene Elkin, Ph.D., and her colleagues (1) raised many important issues in their paper on comparative studies in psychotherapy and pharmacotherapy, nowhere in this paper did the term "transference" appear. It is true that the authors expressed their understanding of the importance of the doctor-patient relationship, but they failed to mention that the patient relates to the doctor in the manner of a child to its parents. This is true whether the mode of treatment is psychotherapy or pharmacotherapy. In both cases the patient has unconscious magical expectations as well as fear of the doctor, whether the latter uses only words or also magic pills. The doctor-patient relationship is an essential ingredient of any form of treatment, and this is totally unavoidable even in treatment that alleges to be only or mainly pharmacotherapy. In point of fact, there can be no pure pharmacotherapy, because transference is omnipresent in the doctor-patient relationship regardless of the treatment modality.

In recent times, a nontransference element in the doctor-patient relationship has also been defined, namely, the therapeutic alliance (ability to work with the doctor). This ap-

years to be more than simply an aspect of positive transference. Regardless of how the treatment alliance is conceptualized, a sense of mutual cooperation must exist between doctor and patient in order for the treatment to progress in a favorable direction. This is as true of pharmacotherapy as it is of psychotherapy, and it is why many therapeutic endeavors fail—the patient or the doctor or both are unable to work together in a cooperative fashion. Most commonly, the problem is the patient's transference hostility, overt or covert. On the other hand, sometimes it is the doctor's countertransference that interferes. Coldness, excessive distance, or authoritarianism on the part of the doctor does not facilitate the formation of a treatment alliance and therefore does not favor the patient's compliance in pharmacotherapy. In addition to being mildly friendly, the doctor must clearly explain to the patient (in a general way) the reasoning behind all pharmacotherapeutic interventions, including the potential benefits and risks. He or she must also be ever ready to adjust the dose if necessary, even giving advice on the telephone at times. In other words, the doctor should do whatever can be done to assuage the patient's natural (transference) fear and to temper the patient's magical expectations. In this way the doctor strives to enlist the patient's cooperation, i.e., encourages a positive transference and also mobilizes whatever capacity the patient has to form a treatment alliance.

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PHILIP KAMINSTEIN, M.D.
Forest Hills, N.Y.

Psychiatric Aspects of Lying

SIR: In discussing psychodynamics in their review of the psychiatric aspects of lies and liars, Charles V. Ford, M.D., and colleagues (1) focused on the conflicts expressed through lies but not on the choice of lies as symptoms. They did not discuss why patients lie instead of channeling their conflicts into some other manifestations.

Clarification of this component of acting-out behavior was provided by Johnson and Szurek (2), who suggested that the choice of behavioral symptoms demonstrated by a patient is often determined by parental expectation, which in turn stems from unresolved parental conflicts around that specific type of behavior. Johnson and Burke (3) later applied this formulation specifically to lying. The following case illustrates this interpretation.

Ms. A, a 21-year-old unmarried woman, referred herself to me for short-term dynamic psychotherapy because of a repetitive pattern of lying that had caused the breakup of a romantic attachment. Her first recollection of lying was early in the third grade. She recalled that, as a recent immigrant, she had felt insecure because of her unfamiliarity with colloquial English and local customs. On the day in question, her mother had given her a dollar for a school function, which was later cancelled. She used the dollar to buy candy for her classmates and told her mother that she had paid it to the school.

When her mother discovered the lie, she was extremely critical and punitive. Furthermore, instead of assuming that the child would learn from the experience, the mother henceforth categorized her as a liar and from that time on made it clear that she expected her daughter to lie at every opportunity. Ms. A consequently became convinced that she had no control over any temptation to lie.

Treatment was focused on helping Ms. A to relinquish her mother's stereotype and to recognize that she had more of a capacity to choose whether to lie or tell the truth than she had been encouraged to believe. In the course of treatment, she recalled several episodes that led her to realize that her mother had often lied, which, Ms. A concluded, accounted for her mother's expectation that she too would lie.

It is crucial in the psychotherapy of acting-out conditions to focus first on closing the control gap, or "superego lacuna," before stirring up the underlying conflict (4). Otherwise, the behavioral symptoms—in this case, the lying—may be exacerbated during therapy, with possible serious consequences to the patient's life situation.

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C. KNIGHT ALDRICH, M.D.
Charlottesville, Va.

Polydipsia and Hyponatremia

SIR: Barbara P. Illowsky, M.D., and Darrell G. Kirch, M.D. (1) presented a valuable review of polydipsia and hyponatremia in psychiatric patients. Reviewing techniques for long-term management, they recommended using fluid restriction and removal of factors exacerbating polydipsic behavior. While these environmental control techniques are likely to be of benefit, an approach directed at training and maintenance of a desired healthy behavior may be more therapeutic. The following case presents such an approach.

Mr. A, a 32-year-old man with diagnoses of organic delusional syndrome, mild mental retardation, seizure disorder, and polydipsia, had been hospitalized in psychiatric institutions for many years, commencing when he was 8 years of age. His physician noted, "The patient appears to have psychogenic polydipsia; indeed, he displayed a cup of normal size (approximately 250 ml), which he indicated he drank water from, 'five cups at a time,' many times a day."

Baseline measures of seizure activity and blood serum electrolyte levels were obtained. A behavioral treatment program was then implemented, in which Mr. A would be able to obtain privileges contingent upon appropriate fluid consumption and maintenance of sodium electrolyte levels within an acceptable range (135-148 meq/liter). Behavioral goals included limiting himself to two daily visits of

no more than 30 seconds to the water fountain, abstaining from carrying a cup or glass, limiting himself during meals to the fluids typically provided, and having sodium electrolyte levels within the normal range. Various privileges could be earned contingent upon attaining these target behaviors. After 4 months of treatment, an 8-month reversal phase followed, in which the previously set-forth privileges were discontinued. Mr. A gradually experienced a reemergence of symptoms, necessitating reimplementa- tion of the treatment program.

During the baseline phase, 80% of Mr. A's sodium electrolyte assays showed levels below 135 meq/liter, the mean level being 129.5 meq/liter. During the treatment phase, only one of 13 measures was below the acceptable range. During the reversal phase, 38% of his sodium electrolyte assays indicated levels below the acceptable range. Upon reinstitution of the treatment contingencies, Mr. A consistently maintained sodium levels within the acceptable range over a 7-month period. In addition, greater variability of sodium electrolyte levels was noted during the baseline and reversal phases. During the treatment phases, Mr. A averaged 2.4 seizures per month, contrasted with 4.8 seizures per month during the no-treatment baseline and reversal phases.

The goal of therapy is the establishment of healthy behavior that enhances one's ability to function adequately, not simply the restriction of unhealthy behavior (2). Reinforcement of patient control over behavior has the added potential of increasing feelings of mastery, self-confidence, and positive self-perception (3). Behavioral principles suggest that combining reinforcement of desired behavior plus inhibition, extinction, and/or restriction of nondesired behavior is likely to maximize therapeutic benefit. This case study also indicates the importance of attending to polydipsia and hyponatremia in patients with seizure disorders, even when the hyponatremia is mild.

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JON E. BENTZ, PH.D.
Lancaster, Pa.

JAMES A. BERGERON, PH.D.
Newtown, Conn.

SIR: Drs. Illowsky and Kirch presented a very good review of polydipsia and hyponatremia in psychiatric patients. I would like to add two comments on etiological questions concerning polydipsia and water intoxication.

In subjects with otherwise normal laboratory findings, differential diagnosis of polydipsia and polyuria includes psychogenic polydipsia, diabetes insipidus centralis, and nephrogenic diabetes insipidus. Distinguishing between psychogenic polydipsia and diabetes insipidus centralis may be difficult sometimes, even given the possibility of measuring plasma levels of ADH by means of radioimmunoassay. It seems that psychogenic polydipsia in some cases may be ac-

companied by impaired ADH activity. The importance of this finding lies in the possible danger of using ADH to treat a patient with psychogenic polydipsia, as if it were a case of diabetes insipidus centralis, and in this way producing in the patient—whose polydipsia continues—a state of water intoxication. I reported such a case myself (1) and found some others mentioned in the literature (2, 3).

Concerning the still not fully understood pathogenetic mechanisms leading to water intoxication, it is very interesting to learn that, in recent years, nausea has been found to be the most powerful nonosmotic stimulus for secretion of ADH, leading to serum levels 10- to 1000-fold higher than the level required to produce maximum antidiuresis (4). One might suggest that on some occasions this contributes to a vicious circle resulting in the syndrome of inappropriate secretion of ADH: a transient overhydration of the body leads to beginning brain edema and concomitant nausea (especially if large quantities of fluid are ingested within a very short period of time), and the nausea stimulates the secretion of ADH, thus preventing normalization of the fluid balance.

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HANS RITTMANNBERGER, M.D.
Linz, Austria

Controlling Auditory Hallucinations

SIR: The article "Auditory Hallucinations and Subvocal Speech" by Peter A. Bick, M.D., and Marcel Kinsbourne, M.D. (1), along with subsequent letters from Richard C. Evenson, Ph.D. (2) and Joseph M. Palumbo, M.D., and Lawrence H. Price, M.D. (3), prompts this letter.

It is now 20 years since Gustafson and I published the paper "Controlling Auditory Hallucinations" (4), in which we attempted to place the phenomenon in an interpersonal context and demonstrated how patients might obtain self-control by any alternative use of the vocal apparatus. It seems an understatement to note that this finding has been slow to penetrate the treatment armamentarium of mental health professionals. However, in view of its fit with the current concept of empowerment and the importance of the psychoeducational movement in the treatment of chronic schizophrenia, it may be an idea whose time has come.

As a historical note, the first method employed to demonstrate to hallucinators that they could control their own voices was influenced by the presence of a sink and a paper cup dispenser in the room being used, hence the rather dramatic use of gargling (very effective, by the way), which was later extended to singing, humming, or simply talking. The "wide-open mouth" technique seems useful in private situations but less socially acceptable than, for example, humming a song.

A few conclusions from experience following the 1968 paper may be noted.

1. Demonstrating to *all* chronic hallucinators that they may gain control over a major symptom certainly harms none and will benefit many. An attempt to do this during an acute or exacerbated phase, however, is not usually helpful. Assisting in bringing about self-control is not a panacea, but it does set the stage for a more self-governed life in the community.

2. Chronic auditory hallucinators may have as many voices as others in the community have personal relationships, that is, 15–30. Therapists intervene in “strange networks” that make up a good part of the interpersonal worlds of these chronically socially handicapped individuals. Many patients will not wish to give up all their voices and may only work to control the most troublesome, especially if no other interpersonal relationships are available through support groups and the like.

3. Therapists who do intensive work with these patients should remember that the silence of chronic interpersonal sensory deprivation may be broken at times by the therapist's positive words reproduced in subvocal speech; thus, therapists may be engaged in extinguishing their own speech when they seek to help their patients control auditory hallucinations.

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GERALD D. ERICKSON, D.PHIL.
Windsor, Ont., Canada

Positive and Negative Syndromes in Schizophrenia

SIR: In view of current controversies about the validity of the distinction between positive and negative syndromes in schizophrenia, and discrepant findings with regard to this dichotomy, the recent article by William T. Carpenter, Jr., M.D., and associates (1) on the concept of deficit and non-deficit forms of schizophrenia is a valuable contribution. We agree that conceptual issues about the relationship between negative symptoms, on the one hand, and chronicity and “schizophrenic deficit,” on the other, are the principal contributors to the present confusion in the field. We feel that another major problem with the distinction between positive and negative syndromes is the current tendency to view them as a dichotomy and as representing distinct subtypes.

In contrast to positive symptoms, negative symptoms tend to be more persistent, less responsive to neuroleptic treatment, associated with poorer social functioning, more likely to be associated with CT evidence of cerebral atrophy, and generally predictive of a poor outcome (2). On the basis of these differences, several authors have suggested that schizophrenia may be divided into positive and negative subtypes. Almost all current studies of positive and negative symptoms explicitly or implicitly accept this model and make compar-

isons between “positive patients” and “negative patients” (and in some cases, “mixed patients”) on various parameters. While these studies employ rating scales for the assessment of positive symptoms (usually, a Brief Psychiatric Rating Scale [BPRS] factor) and negative symptoms (usually, the Scale for the Assessment of Negative Symptoms [SANS]), they do not precisely define the inclusion and exclusion criteria for delineation of the two groups. Are the “positive patients” defined by the presence of positive symptoms (more than a certain BPRS factor score), the absence of negative symptoms (less than a certain SANS score), or both? Similarly, the precise basis for belonging in the “negative patients” group and the delimitation between the two groups are unclear. There are several other problems with this dichotomy. 1) Positive and negative symptoms frequently co-exist, 2) all schizophrenic patients must have had positive symptoms at some time in their histories to receive that diagnosis, 3) negative symptoms of variable severity and duration are present at least to some extent in all schizophrenic patients, 4) both positive and negative symptoms may respond to neuroleptics (3), 5) positive and negative schizophrenic syndromes are not stable longitudinally (4), and 6) the demographic and prognostic implications of positive and negative symptoms differ at different stages of schizophrenia, varying as a function of chronicity (4). On the basis of these observations, positive and negative features cannot be viewed as representing distinct subtypes but may best be viewed as syndromes, representing separate but related pathophysiological processes in schizophrenia.

While we agree with Dr. Carpenter and his associates that multiple factors may contribute to negative symptoms in schizophrenia, the underlying pathophysiological mechanisms may be similar. We have recently proposed that cholinergic excess may be a major mechanism in the production of negative symptoms (5); cholinergic excess may be associated with depressive and parkinsonian symptoms, thereby explaining the partial covariance of negative symptoms with depression and the partial response to anticholinergic antiparkinsonian drugs. The model also provides for an increase in cholinergic activity in association with the dopaminergic hyperactivity that may underlie positive symptoms, thereby accounting for the partial covariance of positive and negative symptoms in the acute phase of the illness and other clinical phenomena.

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RAJIV TANDON, M.D.
JOHN F. GREDEEN, M.D.
Ann Arbor, Mich.

Prevalence of Depressive Symptoms in Different Races

SIR: In a recent report, William W.K. Zung, M.D., and associates (1) compared the prevalence of depressive symptoms in black and white outpatients. They concluded that there was no significant difference between the races in prevalence of depressive symptoms or distribution of symptom severity levels.

Our experience with elderly patients in an inpatient geriatric psychiatry service is that the rate of diagnosis of depression is much higher in white patients than in black patients. The *DSM-III* diagnosis of major depression was made for four (10%) of 42 black patients and for 66 (46%) of 144 white patients admitted to our service. Neither set of data may reflect the true prevalence of depression in the geriatric population. Nevertheless, the age-specific rates reported in the article by Dr. Zung and colleagues seem to indicate a greater prevalence of depressive symptoms in young black patients and a somewhat lower prevalence of these symptoms in the black elderly. In the group who were 18–34 years of age, the depressive symptoms of 17 black patients were classified as moderate to severe and those of 38 as minimal to mild; 131 had no symptoms. In young white patients the corresponding numbers were 14, 55, and 333 ($\chi^2=13.86$, $df=2$, $p<0.01$). In the group aged 65 years and over, the depressive symptoms of 14 black patients were classified as moderate to severe and those of 31 as minimal to mild; 178 had no symptoms. For the white patients the corresponding numbers were eight, 11, and 65. The differences between the races for this age group were not significant.

Such a view of the results seems to us to be more adequate than the general conclusion that there was no difference between the races in the prevalence of depression.

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ELIEZER PERL, M.D.
CURTIS A. BAGNE, PH.D.
DAVID GUREVICH, M.D., PH.D.
Detroit, Mich.

Preference for Alprazolam Over Diazepam

SIR: In a comment (1) on our letter to the Editor (2), Jonathan O. Cole, M.D., and Maressa Hecht Orzack, Ph.D., compared their data on the potential for abuse of a variety of benzodiazepines and methaqualone (as estimated in recreational sedative drug users) with our data for estimating the seeking and liking potential of alprazolam and diazepam in long-term benzodiazepine-dependent inpatients. Our results revealed a significant preference for alprazolam over diazepam in these patients when both compounds were given in hypnosedatively and anxiolytically equivalent doses (3). In the studies of Drs. Cole and Orzack and associates (4), performed with a rather different group of subjects, alprazolam did not seem to have a greater potential for abuse than diazepam. Facilitation of drug intake, however, has at least two driving forces; one is the ability of a drug to counteract withdrawal reactions, and the other is the abuse potential itself. The most reliable data are therefore obtained from subjects with a current history of drug abuse.

A further extension of our preliminary study, performed under exactly the same experimental conditions as previously described (2), has strengthened our preliminary results (Apelt et al., manuscript in preparation). In addition, when the dose of diazepam was kept constant (5.0 mg) and the dose of alprazolam was reduced from 0.5 mg to 0.37 mg ($N=7$), preference for alprazolam over diazepam was still evident but did not reach statistical significance anymore. In the drug choice test, we found that alprazolam was preferred over diazepam in 57% of the evaluations, diazepam was preferred over alprazolam in 21%, and in 22% of the evaluations neither diazepam nor alprazolam was preferred. The scores for "liking" and "seeking" did not differ significantly between alprazolam and diazepam. It is predictable that with further reduction of the dose of alprazolam, diazepam will be preferred. These data indicate that under conditions in which hypnosedatively and anxiolytically equivalent doses of both compounds are administered, alprazolam is clearly preferred over diazepam. This preference is still evident when the dose of alprazolam is reduced below the equivalent dose of diazepam.

As we have already outlined (2), our studies were performed under double-blind conditions. We also pointed out that for patients with benzodiazepine dependency, such studies require the maintenance of a constant state of withdrawal (and a constant level of serum benzodiazepine metabolites). Therefore, the more rapidly metabolized alprazolam was "sandwiched" between two applications of diazepam. However, it is unlikely that the evaluations of alprazolam were due to the influence of diazepam in particular, since the degree of preference of alprazolam over diazepam was found to depend on the dose of alprazolam.

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CLAUDIA SCHMAUSS, M.D.
New Haven, Conn.
SYLVIA APELT, M.D.
HINDERK M. EMRICH, M.D.
Munich, Federal Republic of Germany

Suicide Gestures and Self-Mutilation

SIR: An article by Minna R. Fyer, M.D., and associates (1) noted a high rate of suicide gestures by borderline patients. It would be helpful to know what behaviors were included in the category of suicide gestures and how carefully suicidal intent was probed. This is of interest to me because during my research on self-harm, I discovered that even though *DSM-III-R* lists suicide gestures and self-mutilation as separate behaviors, many clinicians automatically equate the two. In recent publications (2, 3) my colleagues and I have attempted to show that for patients who repeatedly and deliberately harm themselves (many of whom presumably

could be given a diagnosis of borderline personality disorder), most acts of self-harm are morbid attempts to reduce painful symptoms rather than suicide gestures. Because of the negative reactions associated with self-mutilation, many patients have learned that they will be treated more sympathetically by staff members if they confess that their behavior was suicidal. However, serious suicide attempts are frequently encountered in chronic self-mutilators. In my sample of several hundred such patients, a third expected to be dead within 5 years; 57% admitted to having taken a drug overdose and, of these, one-half had overdosed at least four times.

Finally, I would like to compliment the authors for alerting us to the presence of axis I disorders in borderline patients and for noting that these disorders may be easier to treat than the core symptoms of borderline personality disorder. Although the authors were referring to affective disorder and to substance abuse, I would like to suggest that we consider Pattison and Kahan's proposal to shift repetitive self-mutilation to an axis I category (4, 5). While validation of this proposal can come only from further research, I believe that it might have important treatment implications. Psychiatry's therapeutic successes involve axis I disorders. No consistently effective treatment has ever been developed for an axis II disorder.

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ARMANDO R. FAVAZZA, M.D.
Columbia, Mo.

S. Weir Mitchell's Visual Hallucinations as a Grief Reaction

SIR: Dale K. Adair, M.D., and Matcheri S. Keshavan, M.D. (1) commented on the Charles Bonnet syndrome, which involves visual hallucinations of a pleasant or neutral nature in elderly persons "without signs of a dementiform process" but with sensory deprivation such as ocular pathology. They noted that others have reported the syndrome in elderly women after the death of their spouses, and they offered their own case report of a patient with this syndrome whose sensory deprivation in the form of glaucoma predisposed her to visual hallucinations as a symptom of a grief reaction.

Visual hallucinations as grief reactions apparently can occur without sensory deprivation. Of special interest, because he was a distinguished neurologist and neuropsychiatrist, is the description by S. Weir Mitchell (1829-1914) of his personal experience. The clergyman Phillips Brooks, who had been an intimate and beloved friend of Mitchell for many years, died in 1893. Mitchell wrote about it in his unpub-

lished *Autobiography*, and his biographer, Ernest Earnest, drew upon this manuscript for his account. "A reporter brought the unexpected news one morning and Mitchell, greatly shaken, went up to tell his wife. On the way back downstairs he had an odd experience: he could see the face of Brooks, larger than life, smiling, and very distinct, yet looking as if it were made of dewy gossamer. When he looked down, the vision disappeared, but for ten days he could see it a little above his head to the left. The strange incident carried his mind back to the mysterious footsteps heard by his father and mother the night of his brother Alexander's death. Brooks had been one of the two or three friends Mitchell considered really great" (2).

Although the visual hallucinations were clearly related to a reaction of grief without sensory deprivation, Mitchell apparently offered no explanation for the hallucinated figure that appeared specifically "above his head to the left." It would be interesting to know the frequency of hallucinations occurring in persons without sensory deprivation compared with those in persons with sensory deprivation but "without signs of a dementiform process." In Mitchell's case and probably not infrequently in others, the hallucinations presumably constituted a compensatory effort to cope with the drastic sense of loss.

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JEROME M. SCHNECK, M.D.
New York, N.Y.

Source of Freud's Question About What Women Want

SIR: A letter from Lynn Whisnant Reiser, M.D. (1) dealt with a remark of the presumably wisest, wittiest, and most often quoted man of our millenium, Sigmund Freud, as reported by his biographer, Ernest Jones. According to the latter's statement, Freud once said to Marie Bonaparte, "The great question that has never been answered and which I have not yet been able to answer . . . is 'What does a woman want?'" In the original German version, the last four words of Freud's question were, "Was will das Weib?"

In her letter, Dr. Reiser submitted this question to various attempts at explanation without arriving at a convincing solution. As far as I am concerned, the very wording of the question points to the probability that it was a jocularly and popularly used expression of an age-old formulation. My notion is based on the fact that this was a frequent joke, or *Witz* (as the German translation would be), in South Germany, where I lived during the first 30 years of my life and received my medical degree, and which geographically as well as psycholinguistically is close to the Austrian border and the language that Freud spoke in Vienna. The question "Was will das Weib?" reminds me of the often-expressed query "Was will der Kerl?" or "Was will der Bursch?" (i.e., "What does that fellow want?"), which is almost regularly, if often silently, asked with regard to persons—in this case, male—whom one regularly encounters, but who prefer to remain taciturn or semitaciturn during such encounters. Stefan Zweig's famous book *The World of Yesterday* offers many such examples with reference to Viennese women, and

Stefan Zweig was a good and close friend of Freud during those days. Therefore, I do not believe that Freud derived the wording (or its meaning) from his reading of Bernard Shaw, as Dr. Reiser assumed, or from other sources; I think that it was his own quip.

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WILLIAM G. NIEDERLAND, M.D.
Englewood, N.J.

Somatization in Psychiatric Patients

SIR: I wish to comment on the interesting data presented by Shekhar Saxena, M.D., and associates regarding somatic symptoms of Indian psychiatric patients (1). The call for further research regarding the phenomenon of somatization in a variety of psychiatric settings is clearly warranted. In particular, scrutiny of somatization in the United States clearly lags behind that of our colleagues elsewhere. A growing multicultural literature suggests that somatization is, in itself, a major presenting complaint. Much of the research has been carried out by psychiatrists in nations less industrialized than the United States. Thus, it is commonly thought that somatization (either as a primary functional psychiatric disorder or as a component of depressive or anxiety disorders) is quite prevalent in the less economically developed nations but rare in the more industrialized nations. This has led to various hypotheses of social, cultural, educational, ethnic, and mixed etiology.

Caution is warranted in reaching such conclusions. Most crucially, we must await the fuller development of ethnopsychiatric epidemiology. Once the generic aspects of psychiatric disorders in *Homo sapiens* are disentangled from cohort-specific and culturally influenced idioms of distress, firmer etiological conclusions can be drawn. A principal aim must be first to define, by valid and reliable cross-cultural comparisons, the universal features of disorders such as somatization; universality suggests a biological basis. Then, in counterpoint, meaningful discussion of ontogenic (cultural, social, ethnic, developmental, etc.) etiological mechanisms can follow (2).

A secondary note of caution is warranted by the empirical evidence already accumulating. There is a well-established literature documenting somatic complaints among patients in industrialized nations around the world, including the United States (3). Unfortunately, somatic complaints are often overlooked by clinicians and researchers in the large American centers where the widely used diagnostic criteria are developed. Such criteria are limited in descriptive power by this sample bias, reflecting features of advanced cases seen by specialists in tertiary centers.

Indeed, prospective general population surveys are needed to define somatic psychiatric phenomena more fully. Retrospective reviews of psychiatric disorders in an American family practice (4, 5) suggested that somatization is a commonly seen clinical phenomenon and that there are sharp distinctions between the mode of somatization that is a correlate of depression and the mode associated with anxiety. Over a prodromal period, somatization heralded the onset of depression but not anxiety. (While such distinctions were not noted by Dr. Saxena and his colleagues, this may reflect dif-

ferences in study design.) In periods of acute illness, however, the two diagnostic groups in the family practice studied were similar with respect to somatic symptoms.

Somatic symptoms may be alive and well the world over. Further studies such as the one by Dr. Saxena and associates, replicated in a variety of settings, will eventually clarify the biological, economic, social, ethnic, and cultural components.

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DANIEL R. WILSON, M.D.
Belmont, Mass.

Diagnosis of Refugees

SIR: I am writing in response to the article "*DSM-III* Psychiatric Disorders Among Hmong Refugees in the United States: A Point Prevalence Study" by Joseph Westermeyer, M.D., Ph.D. (1). Since the study was on refugees from Asia, I wish to make a few comments from the experience of my colleagues and myself in providing psychiatric care to Afghan refugees in Delhi. Our findings on 152 such refugee patients were published earlier (2).

Dr. Westermeyer found problems in assigning diagnostic categories, since 31% of the subjects "did not fall clearly into any one *DSM-III* category." We used the *ICD-9* classification but faced similar problems, since the concept and description of adjustment reaction (category 309) does not apply well to the majority of these patients (who have symptoms of many years' duration) in spite of our strong feeling that most of their symptoms were stress-induced. The most frequent diagnostic categories in our study were anxiety neurosis (30.9%), depressive neurosis (29.6%), and adjustment reaction (7.2%). Applying *DSM-III* criteria to a subsequent sample of patients, we found that the most frequent categories were generalized anxiety disorder and dysthymic disorder. Most patients did not fit into the posttraumatic stress disorder category because the specific symptoms of reexperiencing the trauma and numbing of responsiveness were not present.

Dr. Westermeyer commented that somatic preoccupation was not observed in his subjects. Our study also revealed that the most common symptoms were psychological and not somatic. Hysteria was diagnosed in only two of the 152 patients. This is in contrast to Indian patients attending the same hospital, among whom somatization is quite common (3) and hysteria is diagnosed in 5%-8% of the outpatients. We have no reason to believe that somatization is less common in Afghanistan. These observations raise the interesting possibility that somatization is less common and anxiety and depressive symptoms are more common in refugees than in the population in their home country. It will require well-

lanned, systematic studies to prove or disprove this hypothesis; however, one of the possible explanations for this phenomenon is that the unusually severe psychosocial stress of uprooting (4) produces definite psychological symptoms which are readily reported, whereas the relatively milder usual life stresses result in somatization in predisposed persons.

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SHEKHAR SAXENA, M.D.
New Delhi, India

Dr. Westermeyer Replies

SIR: Dr. Saxena's similar findings among Afghan refugees in Delhi are most interesting, since they come from a different cultural group seeking refuge in another country. If I were to ignore the stress-inducing aspects of the cases I reported, most of my subjects would also have fitted into the dysthymic disorder category, with a smaller number in the generalized anxiety disorder category. The *ICD-9* classification is more difficult to apply for research purposes, since the criteria are not so highly specified; I hope that *ICD-10* will correct that problem.

It should be pointed out that Dr. Saxena and I used different sampling techniques for our two studies. His study was based on a group of psychiatric patients, while mine was based on an epidemiologic survey of refugees at large in the population who were not seeking psychiatric care. Nonetheless, the similarity in these findings does cast doubt on the relevance of the *DSM-III* system for these patients. As Dr. Saxena points out, the diagnosis of posttraumatic stress disorder is not appropriate either, because many of these patients do not meet the criteria.

There may be some confusion between Dr. Saxena and me regarding "somatization" and "somatoform disorder." In work that has not yet been published, my colleagues and I did see evidence of somatization symptoms in a large minority of our subjects. However, somatoform disorder was not present. In another study of 300 refugees whom we have treated in an outpatient setting, only three (i.e., 1% of the total group) were found to have somatoform disorder. I believe it is important to distinguish between somatoform disorder (or hysteria) and somatization symptoms associated with other psychiatric disorders. In part, this distinction has theoretical implications; even more important, the distinction has therapeutic and prognostic significance.

JOSEPH WESTERMEYER, M.D.
Minneapolis, Minn.

Underrecognized and Underresearched Side Effects of Neuroleptics

SIR: The article by Ruth Dowling Bruun, M.D. (1) on the subtle and underrecognized side effects of neuroleptic treatment is an important contribution concerning the dysphoria and anxiety that can present as serious side effects of neuroleptic treatment. These side effects are especially pertinent when nonpsychotic individuals such as those manifesting Tourette's disorder are treated with neuroleptics. It is clear that the dysphoric reactions associated with neuroleptics can be distressing and, as stated by Dr. Bruun, are "clearly an organic affective syndrome." A great deal of research has been done on the more widely recognized side effects of neuroleptics such as tardive dyskinesia, particularly with animal models showing dopamine receptor supersensitivity. However, the issue of dysphoric and affective changes associated with neuroleptics is not only underrecognized, as argued by Dr. Bruun, but also greatly underresearched. The lack of an appropriate animal model has especially hindered our understanding of the underlying mechanisms and the development of potential treatments for these types of side effects. Unfortunately, since the decreased movements produced by neuroleptics in animals (2) can confound the study of most behavioral indexes of emotionality that rely on motor performance, dysphoric effects of drugs in laboratory animals are rarely reported. In addition, most neuroleptics are tested in animals when they are already in a hyperaroused and/or anxious state, thereby creating a possible ceiling effect for obscuring the observation of further changes in the affective state of the animal. However, a widely underrecognized model of emotionality in rats may be appropriate for studies with neuroleptics.

The most commonly used index of emotionality in rats has been defecation. In 1957 Broadhurst (3) stated that "defecation is the emotionality index of choice in the rat." Similarly, as described by Hall (4), when animals were placed in an unfamiliar or arousing situation, defecation levels exceeded the amount seen in habituated or home-cage environments. Interestingly, most investigators have found a decrease in emotional defecation in response to neuroleptics in rats, supporting the notion that neuroleptics act as "major tranquilizers" (5). Indeed, we and our colleagues demonstrated that the major neuroleptics haloperidol and pimozide decreased emotional defecation when this was measured in a novel environment, as is typically done (6). However, we also demonstrated that these same drugs paradoxically *increased* emotional defecation when the drugs were administered and the response was measured for rats in their home cage or in a habituated open-field environment. The fact that the same dose of haloperidol given to rats either increased or decreased defecation, depending on the environment in which the animals were tested, suggested to us that this effect was not simply due to a peripheral mechanism of the drug on the gastrointestinal system but was due to the emotional state of the animal. Furthermore, when animals were given the peripherally acting dopamine receptor blocker domperidone, no changes in defecation levels were found, supporting the contention that this phenomenon was of central origin and not directly related to blockade of peripheral dopamine receptors (6). In addition, haloperidol-induced defecation could be attenuated by pretreating the animals with the anti-anxiety agent diazepam (6). These data support the contention that haloperidol was causing a dysphoric or anxious reaction in the rats, thereby increasing emotional defecation.

A main point that may emerge from these studies is that

the type of response to neuroleptics can be greatly influenced by both the external and internal environmental states of the animals. Perhaps this is why some individuals experience dysphoric and/or anxious states, rather than the more sedative effects, following neuroleptic treatment. Obviously, it is a large leap from rat defecation to anxiety disorders in humans undergoing neuroleptic treatment, and more research needs to be done to elucidate the mechanisms underlying the affective changes caused by neuroleptics. Nevertheless, we believe that the changes in emotional defecation in rats which are dependent on environmental contingencies provide an excellent animal model of neuroleptic-induced dysphoria and anxiety, which may prove useful for assessing potential therapies with respect to these underrecognized neuroleptic-induced side effects.

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PAUL R. SANBERG, M.D.
ANDREW B. NORMAN
Cincinnati, Ohio

Dr. Bruun Replies

SIR: The observations made by Drs. Sanberg and Norman on emotional defecation in rats are most interesting. The discovery that changes in defecation of neuroleptic-treated rats depend on environmental contingencies seems to indicate that these rats do become dysphoric or anxious. If this is so, then one must postulate either that the rats in their habituated environment are more subject to dysphoria or that exposure to unfamiliar or arousing situations causes sufficient external anxiety to override the internal distress, so that the tranquilizing effect of the neuroleptic becomes dominant.

However, a more complicated question arises when one tries to define what sort of neuroleptic-induced dysphoria the rats may actually be experiencing. Are they victims of an organic affective syndrome consisting of depression with anxiety, or are they experiencing an organically induced anxiety syndrome such as akathisia? Akathisia might be attenuated by pretreatment of the animals with diazepam (1). Its symptom (increased defecation) also might be overridden by the tranquilizing effects of a neuroleptic when external stress is introduced.

Certainly, in human subjects it is often difficult to distinguish akathisia from "real anxiety." The key to this diagnostic dilemma is in the subjective experiences that are related to the physician by the patient (2). Even then, there is much controversy about the true nature of this neuroleptic-induced

extrapyramidal disorder. Is it a mental disorder, distinct from dysphoric reactions to neuroleptics? Is it purely a movement disorder? Or is it a combination of these (3)?

Indeed, the more subtle side effects of neuroleptic treatment are both underrecognized and underresearched. Animal models are much needed in the study of these phenomena, and the discovery by Drs. Sanberg and Norman that neuroleptic response in rats may depend on external influences raises some intriguing questions. Further study of nonpsychotic human subjects will, I hope, provide more insight into the emotions experienced by these enigmatic nonhuman subjects.

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RUTH DOWLING BRUUN, M.D.
New York, N.Y.

Hemifacial Flushing During Unilateral ECT: An Alternative Explanation

SIR: We read with interest the letter "Hemifacial Flushing During Unilateral ECT" by Sudharam Idupuganti, M.D. and Raul Mujica, M.D. (1). The authors reported that the patient experienced flushing and lacrimation during unilateral ECT only on the side ipsilateral to the stimulus (both left and right), as well as bilaterally during bilateral ECT. They attributed this finding to ipsilateral electrical stimulation of peripheral seventh and 10th cranial nerve structures. They further noted, "For unknown reasons, our patient did not have the centrally mediated parasympathetic response," i.e. bilateral response. The ECT procedure the authors described specified use of a cuff applied to the left forearm to monitor right unilateral ECT. (Presumably, although this was not mentioned, the cuff was placed on the right forearm during left unilateral ECT.) Placement of the sphygmomanometer cuff contralateral to the side of stimulation is an improper technique (2), as it does not permit one to monitor for generalized (bilateral) seizure activity. Right unilateral stimulation would lead to seizures on the left side, even in the absence of seizure generalization; however, if seizures are noted on the right side of the body following right unilateral stimulation, then the seizure has definitely generalized. In view of the incorrect cuff placement and absence of any evidence of generalization, it is possible that in the cases reported, unilateral stimulation resulted in unilateral seizures, and an other explanation for the observed ipsilateral flushing and lacrimation is possible, namely, unilateral (nongeneralized) seizure resulting in unilateral central cranial nerve stimulation. As Drs. Idupuganti and Mujica pointed out, flushing and lacrimation are parasympathetic phenomena mediated by the 10th and seventh cranial nerves, respectively. However, all components, including autonomic portions, of these nerves supply facial structures ipsilateral to the side of origin in the brainstem (3). Therefore, stimulation of one-half of the brain (including brainstem) would produce ipsilateral flushing and lacrimation. Another point that supports this contention is the fact that the patient "improved slightly after

the bilateral treatments," which presumably produced generalized seizure activity, unlike the unilateral procedure.

This case emphasizes the need during unilateral ECT for simultaneous monitoring of seizure activity by means of the cuff method, ipsilateral to the side of stimulation, and bilateral EEG electrodes.

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JOHN R. DEQUARDO, M.D.
RAJIV TANDON, M.D.
Ann Arbor, Mich.

Drs. Idupuganti and Mujica Reply

SIR: We thank Drs. DeQuardo and Tandon for correctly pointing out an error in our report; it is our practice to monitor seizure activity by applying a tourniquet to the *ipsilateral*, not *contralateral*, arm during unilateral ECT. We did monitor our patient's *right*, not left, arm during the administration of the right unilateral ECT, and vice versa during left unilateral treatments. We regret the error in reporting. For this reason, the phenomenon of hemifacial flushing during unilateral ECT cannot be explained by incorrect cuff placement.

We agree that bilateral ECT, in most cases, produces a quicker and a more predictable therapeutic effect than unilateral ECT.

SUDHARAM IDUPUGANTI, M.D.
RAUL MUJICA, M.D.
Brooklyn, N.Y.

The Meaning of Empathy

SIR: In his attempt to tease apart the many meanings of empathy, Howard E. Book, M.D. (1) wants to distinguish empathy from mere kindness or unquestioning acceptance and also to distinguish the experience of empathy, which he locates within the psyche of the therapist, from "being empathic," the interpersonal intervention in which the therapist comments on the patient's inner state.

Dr. Book wrote that being empathic is an interpersonal response by which the therapist voices empathic understanding in such a way that the patient feels understood and soothed. But need this be the case? In some instances, might being empathic not entail bringing the patient up short, or prescribing a drug, or remaining silent, or blocking the patient's projection in a way that in ordinary terms would be described (and experienced) as harsh?

"Being empathic" is hard to define precisely because we want to have it both ways: we are reluctant to use the term "empathy" in connection with acts that do not appear kindly. Perhaps we must make a choice. Either we must demand that "being empathic" refer only to explicitly soothing interpersonal acts (and thus lose the potential benefit of cer-

tain acts which arise out of empathy but are experienced as unfeeling, mechanical, or even distancing and rejecting), or we can let "empathic" refer to all appropriate acts arising out of empathy and be willing to reject the common understanding that such acts will be kindly rather than firm. My own leaning is slightly toward the common language resolution (some appropriate acts arising out of empathy just cannot be called empathic), but it is a close call.

I wonder whether even the distinction between empathy and being empathic holds up. Independent of our specific technique, a patient may intuit that we are empathic, and in that case our inner state, however minimally manifested, will have the force of an action. (Consider what happens when a patient comes to understand that his therapist does not feel empathy for him; in that case, "lacking empathy" immediately becomes the act of "being unempathic," whatever the therapist's technical intervention.)

Kohut (2) considered empathy to be a "mode of cognition," which certainly describes one of the things it is. As with any form of cognition, multiple actions—or forms of inaction—may flow from empathy, and I think our profession has great ambivalence, difficult to resolve or even clarify with mere definition, about which among these qualify as empathic.

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PETER D. KRAMER, M.D.
Providence, R.I.

Dr. Book Replies

SIR: From the definition I offered, empathy is one mode of gathering information about the patient's inner world. It requires therapists to place themselves in their patients' shoes by attending to their own internal experiences as they shift back and forth between thinking with and about their patients. Empathy "occurs" within the therapist and has no valence.

Dr. Kramer correctly quotes my definition of "being empathic" as flowing from empathy and referring to the therapist's voicing that empathic understanding so that the patient feels soothed and understood. If the patient does not feel soothed and understood by the therapist's comments, the therapist is not being empathic. The patient is the final arbiter about whether the therapist is being empathic.

I disagree with the suggestion that bringing the patient up short or blocking the patient's projection in a way that would be experienced as harsh is being empathic. In the example of blocking the projection, I would instead wonder what inner experience of the patient fuels his or her need to project at that moment. Patients project when they are feeling frightened, fragmented, accused, or hopeless. It is far more appropriate to respond to the fragmenting feeling before addressing other ways of viewing the situation.

I offer this approach not out of a need to be seen as kindly but because such an approach solidifies the therapeutic alliance, creating a psychotherapeutic milieu that supports exploration of the need to project and ultimately permits the

patient to develop a more reality-based assessment of his or her world.

Consider, for example, the intervention of confrontation. Although it may be an accurate description of a patient's behavior to confront that patient with the statement "You are quite secretive," it is probably not helpful for solidifying the therapeutic alliance or promoting further understanding of this guardedness, since descriptive confrontations are often experienced as reproachful. It is more beneficial to voice empathically the same confrontation as follows: "I sense it is quite difficult for you to feel comfortable enough with me to tell me some of what's on your mind"—an approach that allows the patient to feel understood rather than admonished, strengthens the working alliance, and promotes reality testing.

Dr. Kramer is correct that an act arising out of empathy may be experienced as unfeeling or rejecting. However, this would not be "being empathic"—although it may be clinically necessary. Here I am thinking of the involuntary commitment of patients. Although on occasion such patients never returned to me for psychotherapy and probably did not experience my actions as "being empathic," I was being therapeutic in hospitalizing them at a time when they were liable to harm themselves. I was not at that point concerned about how I was experienced. Certain situations require interventions that override the need to be experienced as empathic. These interventions should not be avoided out of a countertransference need to be seen as kindly.

Dr. Kramer and I agree that therapists should be aware of the temptation, arising from the countertransference, to appear kindly through promoting unnecessary positive transferences, encouraging splitting, or overlooking negative transferences. Often these responses reflect therapists' difficulties concerning their own self-esteem or discomfort in addressing patients' distressing affects.

HOWARD E. BOOK, M.D.
Toronto, Ont., Canada

Ear Wiggling Tics

SIR: The 10 cases of ear wiggling tics in India reported by Matcheri S. Keshavan, M.D. (1), most of which occurred under emotional duress, are not the first such phenomena. Priority of observation of ear tics belongs to that genius of movement recording, Walt Disney, who publicly presented the first case (Dopey) in his classic *Snow White and the Seven Dwarfs* 50 years ago.

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DAVID V. FORREST, M.D.
New York, N.Y.

Dr. Keshavan Replies

SIR: I appreciate Dr. Forrest's interest in the case series on ear tics. Dr. Forrest is correct in saying that the presentation of ear tics by Walt Disney in his classic *Snow White and the Seven Dwarfs* preceded my paper by over half a century. However, this was in animation, and it is unclear whether

Mr. Disney's presentation was based on observation of a live person with ear tics triggered by emotional stress or whether this was another product of Disney's vivid imagination. Ear movements were also subsequently exhibited on the screen by Stan Laurel in his comedies, but these movements were voluntary, unlike those of most of our patients.

In any case, as I pointed out, the credit for the first observation of a live patient with ear tics actually goes to Wilder and Silberman (1), who mentioned a case in 1927 in the German psychiatric literature. This was clearly before Walt Disney.

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MATCHERI S. KESHAVAN, M.D.
Pittsburgh, Pa

Dysthymia and Depression

SIR: Dysthymic disorder in *DSM-III* and its variant, dysthymia, in *DSM-III-R* are important although controversial categories for the diagnosis of nonmajor depressive states. *DSM-III-R* calls this category "dysthymia (or depressive neurosis)" and assigns it the *ICD-9-CM* code 300.40. However, the concept behind dysthymia appears quite different from the concept of neurotic depression. For adults, dysthymia represents "chronic disturbance of mood" of at least 2 years' duration, whereas chronicity is not necessary for the diagnosis of neurotic depression. Neurotic depression "has usually recognizably ensued on a distressing experience" (*ICD-9-CM*), but the description and criteria of dysthymia do not mention any psychosocial stressors. Most stress-induced cases of nonmajor depression would, in fact, be diagnosed as adjustment disorders according to *DSM-III-R*. Anxiety is "frequently present" in neurotic depression whereas the description and criteria for dysthymia do not emphasize anxiety except to say that dysthymia can be secondary to an anxiety disorder. *DSM-III-R* also mentions that dysthymia "usually begins in childhood, adolescence, or early adult life, and for this reason has often been referred to as depressive personality." Indeed, the criteria required for making a diagnosis of dysthymia seem very similar to the description of affective personality disorder (diagnosis 301.1) in *ICD-9-CM*; onset at an early age, chronic depressed mood, low energy, and feelings of hopelessness are common to both.

It has been suggested that the term "neurotic depression" no longer be used clinically because of its vagueness (1) and that the concept of dysthymia be restricted to an early-onset chronic subaffective disorder (2, 3), which is even farther from neurotic depression and nearer to depressive personality.

A rethinking of the most appropriate equivalent *ICD-9* *CM* category and code for *DSM-III-R* dysthymia seems necessary. As it will be quite some time before *ICD-10* and *DSM-IV* are operational, this change should be put into effect immediately, to avoid continuation of unnecessary inappropriate terminology.

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SHEKHAR SAXENA, M.D.
PARTHA SARATH DAS, M.D.
New Delhi, India

SIR: James H. Kocsis, M.D., and Allen J. Frances, M.D., raised some interesting issues about the diagnosis of dysthymic disorder vis-à-vis major depression (1). They expressed concern over an artifactually elevated rate of "double depression" among patients with chronic depression. Because some of the symptoms required for dysthymic disorder may (although they need not) overlap with those of major depression, the authors concluded that the mere addition of a couple of symptoms in such cases will all too easily trigger a diagnosis of a superimposed major depressive episode.

We would like to point out that neither *DSM-III* nor *DSM-III-R* provides clear guidelines for the diagnosis of "double depression." Therefore, it is likely that clinicians are going about this differently. Training in diagnosis at the New York State Psychiatric Institute emphasizes that a superimposed major depressive episode should not be diagnosed when a patient develops only one or two new symptoms from the major depressive episode checklist. The chronic, underlying symptoms of dysthymic disorder, which overlap with those of major depression, must *each worsen* in order to count toward the new syndrome (Miriam Gibbon, M.S.W., personal communication, June 1988). General adoption of this convention could provide uniformity in the diagnosis of "double depression" (2) as well as raise the severity threshold for the diagnosis of major depression when it appears in the context of the chronic, subsyndromal dysthymic disorder. Since *DSM-III-R* notes only that a major depressive episode must "represent a change from previous functioning," greater clarification in *DSM-IV* would be welcomed.

To sharpen the boundaries between the two disorders, Drs. Kocsis and Frances recommended lowering the severity threshold for dysthymic disorder and raising the threshold for major depression. They noted that *DSM-III-R*'s changes in the diagnostic criteria for dysthymic disorder are not clearly in either direction. However, they concluded that "the criteria for a major depressive episode in *DSM-III-R* are essentially unchanged" and that "adjustment upward of the major depression severity threshold will have to await reconsideration for *DSM-IV*" (1).

A reading of the new manual suggests to us, however, that the diagnosis of major depression has been significantly strengthened despite the fact that it remains a heterogeneous category which still encompasses relatively mild as well as extremely severe cases. Although symptom *areas* are unchanged, the anchor points for rating symptoms as significant have been raised, particularly for self-reproach, weight change, and loss of interest or pleasure. Further, the latter symptom can no longer be counted twice toward the syndrome. Generally, instructions are clearer and stricter as regards frequency, duration, and cluster. For example, what *DSM-III* termed "relatively persistent" depressed mood has become depressed mood that is present "most of the day, nearly every day." Exclusion criteria now rule out symptoms

that are due to physical illness, which will make it harder to give some medical patients a diagnosis of major depression. Additional subtle changes in criteria will, if they are noted, affect diagnostic practice. Unfortunately, the existence of clear-cut criteria for the mood disorders does not ensure their use (3).

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EILEEN P. RUBINSON, M.S.W.
GREGORY M. ASNIS, M.D.
The Bronx, N.Y.

Drs. Kocsis and Frances Reply

SIR: Drs. Saxena and Das draw attention to the difficulty of translating the *DSM-III-R* diagnosis of dysthymia to a comparable *ICD-9-CM* diagnosis. We agree that the relationship of dysthymia to the constructs of neurotic depression and affective personality disorder remains unclear. Unfortunately, however, the term "neurotic depression" has been used to denote such a vaguely defined, heterogeneous group of conditions that it probably adds little to the classification of depressions. The relation between early-onset chronic depression and the depressive form of affective personality is on the agenda for discussion by the *DSM-IV* Affective Disorders Work Group. At this time it is by no means obvious which changes are optimal. Decisions will require considerable review of data and discussion by experts in this area.

The suggestion of Ms. Robinson and Dr. Asnis that each symptom of dysthymia must worsen in order to count toward a diagnosis of superimposed major depression seems sensible. We would be interested in data on the reliability and validity of these decisions. It remains to be seen whether the subtle changes in the *DSM-III-R* criteria for major depression will have an actual impact on diagnostic practice.

JAMES H. KOCIS, M.D.
ALLEN J. FRANCES, M.D.
New York, N.Y.

Issues in Personality Disorder Diagnoses

SIR: *Umbrage*: The Advisory Committee on Personality Disorders reported (1) "remarkable controversy" over a proposed diagnosis. The controverters held "that the *diagnosis* (emphasis mine) of masochistic personality disorder was biased against . . . women and victims of abuse."

Implied: In APA, political ends must preempt scientific ones.

Gap: APA becoming just another political entity would leave no credible heir now apparent to foster psychiatry's deriving and applying scientific insights.

Vacuum abhorred: But a successor surely would emerge.

Problematic: The nature of that successor.
Unsettling.

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WILLIAM F. SHEELEY, M.D.
Phoenix, Ariz.

Dr. Widiger and Associates Reply

SIR: Dr. Sheeley's telegraphic style makes it somewhat difficult to decipher the exact nature of his concerns. We certainly do not understand the basis for his conclusion from our article that scientific evidence might have been subordinated to political processes when decisions for *DSM-III-R* were made. The decision whether to include the self-defeating personality disorder category should be based primarily on the category's clinical and scientific merits, but this decision should also be informed by the social implications that might arise from possible sex biases in the definition or the diagnosis of the disorder (1). The question of sex bias is

itself a difficult and controversial scientific problem (2, and unpublished paper by T. Widiger and A. Frances, 1988), with its own extensive literature. In addition, most nosological questions do not have a clear-cut scientific answer, since the research literature is subject to different interpretations. It is, then, important and useful to receive input from various and opposing perspectives. It is our hope that sufficient empirical data will be available to adequately inform the *DSM-IV* task force with respect to the utility and validity of the self-defeating personality disorder diagnosis, and we would welcome specific suggestions from Dr. Sheeley and others regarding this controversial diagnosis.

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THOMAS A. WIDIGER, PH.D.
ALLEN J. FRANCES, M.D.
ROBERT L. SPITZER, M.D.
JANET B.W. WILLIAMS, D.S.W.
New York, N.Y.

Reprints of letters to the Editor are not available.

APA Council Reports

At the fall component meetings of the American Psychiatric Association in Washington, D.C., on Sept. 7–10, the APA councils heard reports from their components. Following are summaries of the activities of the councils and their components.

The Council on Aging

Gene David Cohen, M.D., Chairperson

With this report, the Council on Aging marks its first decade and looks back with pride and pleasure at the positive changes in the field since its first meeting in early 1979. Throughout the decade, our goal has remained consistent: to highlight psychiatry's role for practitioners, policy makers, and the public alike. In the first half of its 10-year lifespan, the council sought to define itself and to define the characteristics that distinguish psychiatric treatment of the elderly from the care rendered by nonphysician practitioners. Today, however, although issues of "turf" and self-definition remain, the council has turned increasing attention to special needs and problems affecting the mentally ill elderly themselves.

Over the decade, as the field of geriatric psychiatry itself has grown, so, too, has the Council on Aging. The council has gained increasing credibility both within the APA and in its involvement with entities outside the organization. Its efforts have resulted in the agreement by APA and the American Board of Psychiatry and Neurology, Inc. to seek establishment of a "certificate of added qualifications" in geriatric psychiatry by the American Board of Medical Specialties. Such a certificate, although substantially removed from the broader issue of subspecialization, will go a significant distance in demarcating the role of psychiatry in the treatment of the seriously mentally ill elderly, a role increasingly sought by other medical practitioners.

In the past 10 years, the council has collaborated with other APA components and offices, other medical organizations, organizations of the elderly, and organizations dedicated to meeting the needs of the elderly. The council is particularly proud of its work with the APA Division of Government Relations and the National Institute of Mental Health on issues related to Medicare, Alzheimer's disease, medical management, and long-term care, and it anticipates continued mutually beneficial collaboration in the future. As the council has grown, its advice and consultation have been sought by an ever-widening circle of organizations and individuals; council members have been asked to participate in conferences of other organizations, at Congressional hearings, and in other forums to raise awareness and to promote broader understanding of the needs of the mentally ill elderly. The council has continued its active liaison with the American Association for Geriatric Psychiatry, the National Voluntary Organization for Independent Living for the Aged (part of the National Council on Aging), the American Association for Retired Persons, and the International Psychogeriatric Association. Further, we look forward to continued involvement in the activities of the American Geriatrics Society and the Gerontological Society.

The council's work in 1988 included development of reports and

presentations of its own and the creation of new components. A council work group headed by Gary Moak, M.D., has developed a layperson's guide to psychotropic drug use in the elderly, which will soon be published as an APA volume through the American Psychiatric Press, Inc. A revised version of the report of the Task Force on Nursing Homes and the Mentally Ill Elderly will soon be brought before the council by a small subgroup of former task force members. A designated work group of the council is working with the Committee on Women to develop a presentation for the 1990 APA annual meeting on issues related to mental health and mental illness in aging women. Yet another work group is considering the scope and content of a charge to a new component to focus on patterns and modes of service delivery to the mentally ill elderly.

In 1988 the council once again sought the advice and counsel of representatives of district branch components on aging by opening its regular meeting at the time of the APA annual meeting to interested APA members. A number of issues before the council and its components—including some of its current task forces themselves—have been brought to the council's attention during those meetings and through other communications. To further enhance this communication, particularly in light of the pending certificate of added qualifications in geriatric psychiatry, the council is considering the publication of regular information in *Psychiatric News*. Members wishing to communicate with the council or to suggest subjects for its consideration are encouraged to contact Dr. Cohen through the APA Central Office and to attend the council's open meeting at the 1989 annual meeting in San Francisco.

The *Task Force on Alzheimer's Disease*, Eric Caine, M.D., chairperson, has been developing a series of statements that are directed at policy makers, the public, and psychiatrists and delineate the specific and crucial role of the psychiatrist in the management of patients with Alzheimer's disease and in the conduct of related research. Completion of this short-term charge was scheduled for the end of 1988. A fact sheet developed by the task force for lay audiences will be published by the Division of Public Affairs as part of its fact sheet series. A pamphlet for public policy makers has been distributed by the Division of Government Relations, and an editorial for psychiatrists appeared in the December 1988 issue of the *American Journal of Psychiatry*.

The *Task Force on Reimbursement Options and Alternatives in the Psychiatric Care of Older Persons*, Howard H. Goldman, M.D., chairperson, has undertaken a number of activities. The task force members are developing a broad background paper that details what

constitutes an appropriate care system for the mentally ill elderly and have suggested that the Council on Economic Affairs or Office of Economic Affairs develop a corollary document which would articulate a financing plan for this care system. The task force is investigating holding a conference on these issues in early 1989.

Three new components established in 1988 made considerable headway in fulfilling their charges. The *Task Force on Ethnic Minority Elderly*, Kenneth Sakauye, M.D., chairperson, will try to complete an annotated bibliography in the area by its next meeting, develop a list of high-priority areas for more in-depth work, and develop a list of contacts (including liaison with appropriate APA components). Among specific projects to be undertaken are an evaluation of the Epidemiologic Catchment Area Program tapes for ethnic breakdown and age and a joint component workshop for the 1989 annual meeting.

The *Task Force on Education and Training in Geriatric Psychiatry*, Charles Shamoian, M.D., chairperson, reviewed materials collected and circulated by its members regarding existing training programs and training models. It expressed concern about whether the models are being employed in existing training programs at the medical school, residency, and fellowship levels and, if not, why not. While not intending to reinvent the wheel, the task force is trying to develop appropriate mechanisms to ensure psychogeriatric content at the medical school, residency, and fellowship levels and to develop an appropriate continuing education component to help psychiatrists prepare for the examination for the certificate of added qualifications in geriatric psychiatry.

The *Task Force on the White House Conference on Aging*, Sanford I. Finkel, M.D., chairperson, held its first meeting at the 1988 fall component meetings and focused on the need to attend to such issues as training, manpower, incentives to choose careers in geriatric psychi-

atry, program standards, and the training of primary care physicians in mental health issues. Continuity of care and the need to eliminate Medicare discrimination against both the mentally ill and physicians also arose. Whether miniconferences will be convened by the White House Conference on Aging remains an open question. Nonetheless, the task force is investigating a multidisciplinary meeting along the lines of the past miniconference on mental health and the elderly.

A fourth new task force, the *Corresponding Task Force on Geriatric Psychiatry in the Public Mental Health Sector*, Barry Fogel, M.D., chairperson, held a preliminary meeting of members who were attending the 1988 fall committee meetings for other purposes. Until outside funding is received, the task force will function as a corresponding task force. It was decided to focus on a number of issues specific to the elderly in public sector mental health facilities (predominantly state hospitals): 1) the boundary between physical and psychiatric care for the mentally ill elderly, 2) aftercare for the deinstitutionalized mentally ill elderly, 3) mechanisms of access to the public sector system, 4) the validity of diagnoses of the mentally ill elderly in public institutions, 5) legal issues involved in commitment and in urgent medical care of the mentally ill elderly, 6) active treatment versus custodial care, 7) use of psychotropic drugs and drug-related morbidity, 8) the availability and use of ECT, and 9) the various models among the states for enhancing financial support of psychiatric services for the mentally ill elderly. The task force intends to review the literature, clarify the issues further, and undertake surveys of both facilities and practitioners in public sector sites to evaluate the variability in support, standards, and practices.

Finally, the Council on Aging notes with regret that Teddi Fine, who has served as council staff liaison since the council's inception a decade ago, is "retiring" from APA. We will miss her strong administrative skills and her thoughtful policy advice.

The Council on Children, Adolescents, and Their Families

Larry B. Silver, M.D., Chairperson

This past year the council has again directed efforts toward maximizing APA's effectiveness in addressing the mental health needs of children, adolescents, and their families. A number of these efforts pertain to liaison activities. Dr. Henry Work continued to represent APA at the meetings of the National Consortium for Child Mental Health. Dr. Jeanne Spurlock served as the liaison to the Prevention Coalition of the National Mental Health Association and represented APA at the AMA conference "Adolescent Health: The Roles of Government, Business, and Foundations" and at the AMA National Congress on Adolescent Health. Effective liaison with the Board of Trustees and the Assembly of District Branches has been accomplished through the efforts of Drs. Lawrence Hartmann and Cynthia Rose, respectively. The council has been kept abreast of all government programs pertaining to children and adolescents by Dr. Michael Fishman, who was reappointed as consultant to the council. The informal caucus of child and adolescent psychiatrists held during the APA fall component meetings has also served as a significant liaison, allowing exchange of information about the programs of the American Academy of Child and Adolescent Psychiatry, the American Society for Adolescent Psychiatry, and the APA child and adolescent programs.

Dr. Andre Derdeyn, chairperson of the now disbanded Task Force on Clinical Assessment in Child Custody, assumed leadership in the updating of *Child Custody Consultation*. The large number of requests for copies of this report indicate the enormity of the problems

related to child custody and the apparent usefulness of the report. The council expressed appreciation to Timberlawn Hospital and Dr. Doyle Carson and to the Division of Child Psychiatry, Duke University School of Medicine, and Dr. John Looney, who have agreed to provide funds for printing.

The council received the final draft of the report of the *Corresponding Task Force on Confrontational Therapies*, Mark Blotcky, M.D., chairperson, and will work toward a final product. Letters of appreciation were forwarded to members of the task force, and it was recommended that the task force be disbanded.

The council responded favorably to the report of the *Committee on Juvenile Justice Issues*, William Buzogany, chairperson. Suggestions for some minor editorial changes were forwarded to the committee. It was anticipated that the final report would be ready for publication before the end of 1988. The report identifies points in the juvenile justice system at which clinical intervention is desirable and highlights some of the problems in meeting needs. Suggestions are offered about methods for overcoming the difficulties. Relevant training, research, and public policy issues are also addressed.

The Committee on Juvenile Justice Issues, the Committee on Family Violence and Sexual Abuse (Sandra Kaplan, M.D., chairperson), and the Committee on Psychiatry and Mental Health in the Schools (Irving Berkowitz, M.D., chairperson) held workshops during the 1988 annual meeting and have submitted abstracts for presentations at the annual meeting in 1989. The Task Force on Psychiatric As-

pects of the New Reproductive Technologies (Miriam Rosenthal, M.D., chairperson) also submitted an abstract for a workshop at the 1989 annual meeting.

The council anticipates receiving documents from the Committee on Family Violence and Sexual Abuse, the Committee on Psychiatry and Mental Health in the Schools, and the Committee on Chronically Ill and Emotionally Handicapped Children (Cynthia R. Pfeffer, M.D., chairperson) before the end of 1988. These documents are being prepared as educational materials for psychiatrists and other mental health professionals.

During the course of the year, the Council on Children, Adolescents, and Their Families was represented in two important hearings. Dr. Silver presented testimony on child health programs (including mental health) to the U.S. Senate Finance Committee. Dr. Spurlock focused on chronically mentally ill children and adolescents in testimony presented at the National Council on the Handicapped forum "Living Arrangements for Severely Disabled Children."

The council reviewed the pamphlets on Mental Illness Awareness Week that concerned children and youth. The content was impressive,

but the council found the bibliography inadequate and expressed interest in contributing to such materials that are developed in the future.

The council recommended that there be no new American Board of Psychiatry and Neurology subspecialties in psychiatry but that criteria be established for qualification in specific areas and certificates of special competence in the particular subspecialties be provided for those who qualify.

Several topics were identified for future study: 1) infant psychiatry, with a particular focus on the impact of Public Law 99-457—the Education of the Handicapped Act Amendments of 1986, 2) child care, working mothers, and parental leave, 3) adoption, severance of parental rights, and foster care, 4) substance abuse, and 5) managed care and case management in public health care settings. The council will continue to maintain contact with the leadership of the American Academy of Child and Adolescent Psychiatry and the American Society for Adolescent Psychiatry to assure that the council's undertakings do not duplicate the efforts of these two national organizations. The council is also alert to problem areas concerning children and adolescents that may or should be addressed by other APA components (e.g., Committee on Drug Abuse, Committee on Alcoholism). Active liaison with these components will be reinforced.

The Council on Economic Affairs

Donald J. Scherl, M.D., Chairperson

The year 1988 was a milestone in the economics of psychiatry. Most dramatic has been the movement toward reform of current physician reimbursement systems, which has significant implications for medical care in this country. The Board of Trustees created a new study group under the Council on Economic Affairs to address the Harvard Resource-Based Relative Value Scale Study. The goals of this study group are to 1) review the Harvard study and related fee schedule issues and examine their possible implications, 2) assist with the development of any rapid responses to legislative and/or administrative action based on the study or related to it, as well as any emerging interpretations and potential methods for implementation formulated by governmental regulatory bodies or insurance companies, 3) monitor the responses to the study and actions taken by other medical specialties, and 4) develop policy options for the association to consider in its response to the American Medical Association or other organizations, to Congress, and to the executive branch of the federal government. The issue of physician payment is expected to be addressed by the next Congress.

The council continues to foster nondiscriminatory mental health insurance coverage, to collaborate with other APA components involved in carrying out educational programs for purchasers of health insurance, to articulate and promote fair and adequate standards of practice, to oversee the development and refinement of quality assurance programs, and to identify needs and resources for data related to these tasks. The Oversight Subcommittee of the council, established in 1987 to provide additional member oversight of the quality assurance programs, continues to be active.

In addition to the assistance provided by the Office of Psychiatric Services, the council and its components look to the Office of Economic Affairs for major technical support of their activities. The Office of Economic Affairs is engaged in a number of efforts, including gathering and disseminating information, creating and maintaining specialized data bases, research and special projects for various committees and task forces, and technical assistance, such as helping members to deal with such issues as alternative delivery systems. The office gathers information on psychiatric coverage and puts together

information on trends and statistics. New computer software has been installed that makes abstracts, articles, and other information readily available to members. A marketing specialist was hired in 1988 to develop an overall marketing strategy for the association and to assist district branches in their marketing efforts. *Ecofacts*, the quarterly newsletter produced by the office, has met with resounding success in its first year of publication.

Through the existing committees and task forces on financing and marketing, prospective payment, future trends in private insurance, Social Security disability insurance, psychiatrist payment, hospital-based and hospital-related psychiatric services (standards and accreditation), interprofessional affairs, and quality assurance, the council is able to address a wide variety of economic issues as they affect both our members and our patients.

The *Task Force on Psychiatrist Payment*, Boris Astrachan, M.D., chairperson, was established to examine the nature of psychiatrists' income, including the diversity of practice settings, sources of reimbursement, costs associated with various types of practice, the impact of public and private coverage policy, and the ramifications of changes in health care organization. Data from initial research will be published in a paper titled "Development of Background Data on the Economics of Psychiatric Practice" and will be presented to the membership in a workshop at the 1989 annual meeting in conjunction with the Work Group on Codes and Reimbursements. The task force will continue to work with the Office of Economic Affairs in developing a series of background papers on various aspects of the economics of psychiatric practice. The first of these is titled "Medicaid, Disability and Psychiatry" and covers such areas as the disproportionate significance of Medicaid to the mentally ill, access and coverage issues, regulatory issues, and reimbursement issues. The task force is also working with the Office of Manpower to analyze data on payment and continues to monitor public and private reimbursement policy issues.

The *Task Force on Future Trends in Private Insurance*, Robert Gibson, M.D., chairperson, was formed to monitor emerging issues in private health care insurance and examine their implications for

psychiatric benefits. The task force is developing a series of white papers to describe these emerging trends and their attendant issues, assess their pros and cons, and generally educate the membership as to what might be expected from such trends. The first of these papers will address medical management services performed by psychiatrists, the development and implementation of outcome studies in psychiatry, and public acceptance of psychiatric treatment. The task force has also been charged with examining restrictions placed on life and health insurance on the basis of prior psychiatric treatment.

The *Task Force on Prospective Payment Issues*, Joseph T. English, M.D., chairperson, has continued to monitor prospective payment issues and explore potential alternative payment mechanisms. A series of studies contracted by the task force has been completed and will be enormously useful for the documentation it provides in such areas as the effects on hospitals of changes in the federal diagnosis-related group (DRG) system and the impact of DRGs on the disabled nonelderly under Medicare, which disproportionately affect minority populations. An article titled "General Hospital Inpatient Care: Medicare Experience With the Chronically Disabled" will be submitted for publication shortly. The task force continues to monitor studies by the National Institute of Mental Health on improvement of the DRGs and better ways to reimburse hospitals under a prospective payment system, as well as federal legislative and administrative activities related to prospective payment for psychiatry.

The *Committee on Financing and Marketing*, Robert O. Friedel, M.D., chairperson, finished the National Education Project, which was conducted in conjunction with GLA Associates. The committee placed considerable emphasis on the development of an internal marketing plan for APA, including the hiring of a marketing specialist to work from the Office of Economic Affairs. The marketing efforts included development of a primer on marketing for the district branches, continued technical assistance to the district branches, and distribution of information on ways to approach the business community and employee assistance programs regarding psychiatric services.

The *Task Force on Social Security Income/Social Security Disability Insurance*, Arthur T. Meyerson, M.D., chairperson, remained active throughout the year. The Social Security Administration's listings for mental impairment were scheduled for review, and the task force helped to ensure psychiatric representation on the review panel. Efforts continue to elicit publication by the Social Security Administration of the child listings for disability. In addition, the task force has become involved in the controversy over implementation of the Nursing Home Reform Act, which would prohibit the majority of psychiatric patients from residing in nursing homes that receive Medicaid funding.

The report of APA's Social Security Research Project was accepted by the Social Security Administration. The Task Force on Social Security Income/Social Security Disability Insurance, in conjunction with the Office of Psychiatric Services and the Social Security Administration, again offered its seminar on disability evaluation at the APA annual meeting. The presentation also has been scheduled for the 1989 annual meeting in San Francisco.

The *Committee on Interprofessional Affairs*, Mildred Mitchell-Bateman, M.D., chairperson, has remained active in a number of interprofessional initiatives. Representatives of the committee attended the Seventh Annual Leadership Conference of the Joint Commission on Interprofessional Affairs in April 1988. This commission is a consortium of representatives of APA, the American Psychological Association, the American Nurses' Association, and the National Association of Social Workers. Two elected officers and the executive director of each of the four organizations attend the annual leadership conference. In addition, the four executive directors meet quarterly to discuss issues of mutual concern.

The Joint Commission on Interprofessional Affairs continues its work on two major initiatives: stimulation of counterpart organizations at the state level and development of a consumer-oriented publication on mental health services to be offered by these four organizations. A consumer brochure on insurance coverage for mental health services that was developed by the Joint Commission on Interprofessional Affairs will be released soon. As part of a commission initiative, APA's Committee on Interprofessional Affairs, in consultation with representatives of numerous APA components, is striving to better define psychiatric practice.

The *Committee on Quality Assurance*, George Wilson, M.D., chairperson, has been particularly active during the past year. By mutual agreement, APA and Intracorp did not renew their contract for mental health review services. As of Sept. 20, 1988, APA is free to market its review services at large. A market analysis conducted by outside consultants revealed that APA has the potential to be a strong competitor in the field, and a number of prospective clients have indicated an interest in contracting for service with APA.

As a leader in the field, APA will continue to set the standards for mental health review services. APA's psychiatrist-to-staff ratio is higher than that of other leading review service providers; this "peer review" feature will continue to be one of the hallmarks of APA's quality assurance programs. Written inpatient review criteria will continue to be refined, and the criteria sets, such as those for residential treatment, child and adolescent treatment, and long-term hospitalization, will be expanded. An expert review panel will assess the most difficult and contentious cases. The peer review manual will be revised and reformatted, and development of a quality assurance information service to provide state-of-the-art information on review criteria and procedures is being explored. The Council on Economic Affairs will carefully monitor these developments, as well as quality assurance programs as a whole, over the coming year.

The *Committee on Hospital-Based or Hospital-Related Psychiatric Services*, Boris Astrachan, M.D., chairperson, reviewed a number of proposed changes in the standards of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). The joint commission is actively pursuing its "Agenda for Change" and making major revisions in many of its policies and procedures as a result. The committee has been monitoring these developments carefully, as some have far-reaching implications for psychiatry. In addition, the committee has been involved in a group effort with the National Association of Private Psychiatric Hospitals and the American Hospital Association to develop clinical indicators for psychiatric care.

The Council on Internal Organization

Ronald A. Shellow, M.D., Chairperson

The council represents the membership by overseeing "all those matters involved in the organizational structure of the Association not covered by constitutional committees." There are 12 components that report directly to the Council on Internal Organization

and 16 components that report to committees under its purview. As a result, the council oversees a wide range of activities, such as program content, exhibits, and arrangements for the annual meeting; advertising policies of the Association; data processing, telecommu-

nications, and other information systems within the Association; benefits offered to APA members, such as the legal consultation plan, retirement programs, life, accident, and health insurance, practice management seminars, and financial planning services; all personnel and staff benefit programs; the various prizes and awards presented for outstanding achievement; and the federation of auxiliary organizations. The following items highlight the work of the council and its components over the past year.

The *Scientific Program Committee*, Allan Tasman, M.D., chairperson, reported that the 1988 annual meeting in Montreal was judged successful in terms of program quality, program content, income, and attendance—it was the best attended meeting in the history of the Association. Such overall stability and success have made possible a needed increase in annual meeting fees for participants in 1989 and for industry-sponsored symposia in 1990. Policies that diminish distractions from the importance of the meeting and that preserve the committee's freedom of judgment in selecting material for the program continue to be emphasized by the council. Ongoing consideration of how to encourage participation by a broad spectrum of the membership is reflected in such measures as the Association's provision of day care at the annual meeting.

The report of the *Committee on Advertisers and Exhibitors*, Henry H. Work, M.D., chairperson, indicates that much of the notable success of the annual meeting exhibits can be attributed to diligence in maintaining good relations with the advertisers and exhibitors. Review of the Montreal meeting has led to implementation of policies directed at further improvements in APA-exhibitor communications and at preserving decorum on the exhibit floor. Action was also taken by the council to have exhibitors conform to APA policies regarding discrimination in employment practices.

As chairperson of the *Committee on Advertising*, William D. Strathmann, M.D., now serves as a liaison to the Committee on Advertisers and Exhibitors. This trial measure is intended to increase communication and collaboration between the two committees. Over the course of the year, proposed advertisements for APA publications raised a number of issues that required review by the Committee on Advertising.

The PIA Foundation Hospital Research Award has been revised by the *Committee on Grants and Awards*, Alan I. Levenson, M.D., APA Treasurer, chairperson. The award will now be presented to a senior researcher who will help support a young research psychiatrist. Other priority items for the committee were the refinement and negotiation of a proposal for an award for the study of the Holocaust and genocide and continuing review of methods for maintaining the solvency of existing award funds.

The *Personnel Committee*, Maurice J. Martin, M.D., chairperson, has presented policies for a personnel manual and has assisted in the improvement of the retirement program for the more than 300 APA

employees. The committee mourns the death of its past chairperson, William R. Sorum, M.D.

Presentation of a major program at the Osler Library in Montreal in conjunction with the annual meeting was a primary focus of the *Committee on History and Library*, Lucy D. Ozarin, M.D., chairperson. Other areas of committee involvement included the ongoing transcription of the oral history tapes of past leaders of APA into a more permanent, written form and dedication of the Marion Kenworthy Learning Center at the APA Library in September 1988.

Ensuring the quality of the members' health insurance program remains a principal obligation of the *Committee on Member Life, Accident, and Health Insurance*, Harvey Bluestone, M.D., chairperson. Among additional concerns addressed by the committee was separation of the premiums for accidental death and dismemberment coverage from the premiums for life insurance. Improvement in communications between the committee and Professional Risk Management Services, Inc., is expected to continue, and more active marketing is being done to raise the number of program subscribers. These efforts should facilitate increasing the quality of the programs.

The *Committee on Special Benefit Programs*, Abram M. Hostetter, M.D., chairperson, has concentrated on the development of several pilot programs—one for a financial planning service for members and another for seminars on career choices in psychiatry, to be directed at residents. Maintaining the practice management seminars has also been a primary focus of the committee.

The *Committee on Telemedical Services*, Jane H. Preston, M.D., chairperson, has been greatly involved in designing interactive video programs for nursing homes and the criminal justice system in Texas. Details of a demonstration project in telemedicine, to be underwritten by the Upjohn Company, continue to receive the committee's attention.

According to the report of the *Committee on Friends of the APA*, Evelyn P. Ivey-Davis, M.D., and V. Terrell Davis, M.D., cochairpersons, the APA Auxiliary has been actively networking in the areas of government relations and public affairs. Benevolent projects for seriously ill psychiatrists and their families have received the special attention of the Auxiliary.

Reports were not received from the Headquarters Committee and the Committee on Information Systems.

In addition to its own components, the Council on Internal Organization worked with the Joint Commission on Government Relations, the Committee on Continuing Education, the Ad Hoc Committee on Subspecialization, the Task Force on DSM-IV, and the Work Group on Codes and Reimbursements.

The council noted with great regret the death of its long-time member Walter Tardy, M.D.

In conclusion, the Council on Internal Organization not only welcomes but needs the input of the members to provide them with quality representation in the business and internal workings of the Association.

The Council on International Affairs

Harold Visotsky, M.D., Chairperson

The Council on International Affairs has given high priority to addressing the fact that APA's "Statement of Mission, Goals and Objectives" has no international focus, and it has brought this omission to the attention of the joint Reference Committee. The international activities of the Association are essential as our world becomes smaller and communication among nations even more important. The council has previously asked for some action by the

APA leadership in this respect and hopes that some action will be taken this year. The council continues to express its concern about the level of APA activities in the international arena and the fact that the budget allocations for these activities do not correspond to the requests made, particularly in the area of staffing.

The council works closely with the APA Office of International Affairs in monitoring activities of the Association that go beyond our

national boundaries. In addition to participation in the activities of the council components, the council offers a wide variety of services to colleagues in the United States and abroad. The office refers patients who are traveling or moving to psychiatrists in other countries and furthers scientific exchange and collaboration with our colleagues abroad. In the past year, it has communicated with individuals and organizations in over 60 countries. Our international component has made great strides over the years in furthering the knowledge about American psychiatry abroad and has attempted to further the knowledge in our own country of psychiatric advances made in other countries.

In the upcoming year, the council will focus much of its attention on suggestions about priorities for our Association in the international arena. It is hoped that our ties with many international psychiatric and mental health associations will be strengthened. In the past, APA has been particularly active in the World Psychiatric Association (WPA) and will continue to be very involved as we approach the VIII World Congress of Psychiatry, which will be held during October 1989 in Athens. However, the council also believes that it is important to collaborate with a number of other international organizations and will concentrate on suggesting an overall agenda which will broaden our involvement with these other groups. It is hoped that the WPA will be reorganized in a way that will broaden its activities. The APA leadership will soon be discussing concrete recommendations to be made to the WPA General Assembly next October.

The council continues to be involved in the International Scholars Program for the APA annual meetings and is implementing recommendations to increase the services offered to our international visitors at these meetings. It is important to continue to attract large numbers of participants from other countries as this is a vital educational event in psychiatry.

The *Task Force on International Education*, Normund Wong, M.D., chairperson, has been conducting serious discussions with the leadership of the International Medical Scholars Program, Inc., which is administered by the Educational Commission on Foreign Medical Graduates. This project was being formulated at the same time that the APA Task Force on International Education was working on a similar proposal for consideration by the APA leadership. It appears that it will be more feasible for APA to cooperate with the International Medical Scholars Program in a combined effort to further our mutual goals. It seems that the leadership of that program welcomes the possibility of APA providing the psychiatric component for this new project, which will provide opportunities for certified foreign medical graduates (FMGs) from around the world to study in the United States for 6 months to 3 years with the stipulation that they return to their countries of origin. In the case of psychiatry, these would be certified psychiatrists in midcareer who are outstanding physicians in their own countries, and they would be nominated by their universities or governments. A proposal will soon be submitted to the International Medical Scholars Program for APA to provide a consultation to the organization. Applications will be accepted for the program around early 1990.

The *Task Force to Plan the Joint Meeting in China in 1988*, Herbert Pardes, M.D., chairperson, organized the excellent scientific meeting held in Beijing during August 1988. Approximately 160 Americans and 200 Chinese participated in the meeting, which covered a wide variety of topics. The council was pleased with the ongoing collaborative work between APA and the Chinese Medical Association and the Chinese Society of Psychiatry and Neurology and believes that continuation of this collaboration should be encouraged. This was a particularly important meeting for our Chinese colleagues, who represented every province in that country, because it was the largest psychiatric meeting ever held in China.

The *Task Force to Plan the World Psychiatric Association Regional Symposium*, Robert Hales, M.D., chairperson, was pleased with the outcome of that congress, held on Oct. 13-16, 1988, in Washington, D.C. The scientific program, titled "The Research and Clinical Interface for Psychiatric Disorders," featured invited plenary speakers on the following topics: "An Update From NIMH," "Affective and Anxiety Disorders," "Schizophrenic and Organic Disorders," and "Towards an Integration of Nomenclature and Psychiatry." We were delighted to have Dr. Gerald Klerman as the

keynote speaker at the opening session and Sir Martin Roth as the Distinguished Lecturer at the closing session. In addition, there were simultaneous symposia, paper sessions, and poster presentations, for a total of over 300 presentations from 32 different countries. There were over 700 participants from around the world.

The *Committee on Abuse and Misuse of Psychiatry and Psychiatrists*, Michael Zales, M.D., chairperson, continues to work diligently on its charge by having meetings and/or conference calls every 6 weeks. The committee continues to address allegations of abuse of psychiatry from a variety of countries even though the ongoing focus is still on the Soviet Union, which appears to be the only country that systematically uses psychiatry for political purposes. One major task of the committee in coming months will be to discuss a recommendation for APA's position on the possible readmission of the All Union Society of Psychiatrists and Neuropathologists of the U.S.S.R. to the WPA. The committee has noted that a resolution on this subject has already been passed by the Royal College of Psychiatrists of Great Britain:

Recalling the General Assembly's resolution of 1977 and 1983 about the abuse of psychiatry for political purposes, the Royal College of Psychiatrists proposes that the All-Union Society of Psychiatrists and Neuropathologists of the USSR should only be invited to rejoin the World Psychiatric Association when the following conditions have been met:

1. The Authorities have dissociated themselves from the past abuses and taken effective action to prevent their repetition.
2. All individuals detained unjustifiably in psychiatric institutions have been released.

The committee has not decided whether to recommend that APA take a position at this time, particularly since approval has been granted for a delegation of American psychiatrists to travel to the Soviet Union to examine former and present psychiatric patients who are believed to have been incarcerated for political rather than medical reasons. This trip resulted from the initiative of the U.S. Department of State and the U.S.S.R. Ministry of Foreign Affairs, and the work of the delegation is being discussed in conjunction with the U.S.S.R. Ministry of Health, the National Institute of Mental Health, and APA. It is hoped that the delegation will be able to visit the Soviet Union in early 1989. An advance team will negotiate the list of stipulations, which will have to be agreed on before the visit of the specialists who will actually interview the individuals in question. There will also be discussions about the guidelines for involuntary hospitalization in both countries. The committee and the council are pleased with the negotiations to date and look forward to receiving additional information as it is available. It is clear that this delegation will not discuss policy implications for any of the organizations involved but will, rather, complete a report which will be distributed to the organizations as background material for their own discussions regarding policy.

The committee continues to have a liaison relationship with the APA Committee on Human Rights and the Committee on Abuse and Misuse of Psychiatry in the United States.

In the past year, the *Committee on Human Rights*, Lawrence Hartmann, M.D., chairperson, has worked on a wide variety of issues having to do with the medical and psychological implications of human rights abuses in many countries. The committee was disappointed that the South African government rejected the visa applications for the mission being organized by the American Association for the Advancement of Science, in conjunction with APA, the National Academy of Sciences, and the American College of Physicians; the mission was to have taken place in April 1988. The rejection of the visas was announced by the South African embassy on the day of the planned departure. These organizations continue to plan such a visit, and it is hoped the visit will take place in early 1989.

The committee has proposed that APA establish an APA Human Rights Award, which would be given to an individual or organization exemplifying the noble, often selfless, and sometimes dangerous capacity of human beings to protect their brethren from arbitrary and unjustified damage at the hands of other human beings. It is hoped that the award would consist of a statement, suitably written and presented, which would be given to the recipient either at the

annual meeting or on some other occasion during the year and publicized through official APA publications. The recommendation states that this could be an annual award but should be given only if an appropriate recipient is available. This recommendation has been endorsed by the council and the joint Reference Committee and has been referred to the Committee on Grants and Awards.

The *Task Force on Problems of Americans Overseas*, Eric Plaut, M.D., chairperson, has completed its main task of organizing the 1986 conference "Living Abroad: Adjustments and Crises" and has continued to function at no expense to APA since that time. It had hoped that another, more multifaceted organization would undertake a project dealing with the problems of Americans overseas and that APA could provide the psychiatric component. Unfortunately, this goal has not been reached, even though the task force has maintained contact with the many interested parties from the 1986 conference. Thus, the task force is being disbanded with appreciation for its diligent work and efforts. The task force has notified the network of individuals and organizations involved in these issues that it is being disbanded but that APA maintains its interest in this area and would be happy to consider collaboration on a larger project if and when it is established by another organization. The funds generated for this project will now revert to the APA general fund.

The *Task Force on Terrorism*, L.J. West, M.D., chairperson, organized an outstanding symposium for the 1988 annual meeting in Montreal that was well attended and attracted much interest. However, the task force has not been able to formulate a larger project in the realm of APA and, since its tenure was limited, is being disbanded with appreciation. It is hoped that some of the issues addressed by this component will be covered under the new proposal for a component on conflict resolution, which will be mentioned later in this report.

The *InterAmerican Council of Psychiatric Organizations*, Evaresto Gomez, M.D., APA delegate, continues to work on improving communication and collaboration among psychiatrists in the Americas. New officers have been elected and a secretariat established in Washington, D.C. Whenever possible, the members of the InterAmerican Council hold meetings in conjunction with major scientific meetings, and they have proposed a symposium to be held at the APA annual meeting in San Francisco, titled "Stigma in the Americas." The InterAmerican Council continues to appreciate the support of the Pan American Health Organization and the APA Office of International Affairs for their ongoing efforts to further its vi-

bility. It is hoped that as its membership increases in various countries there will be more collaboration and communication. Its activities presently take place at no expense to APA.

The *Task Force on Psychosocial Aspects of the Middle East Peace Process*, George Tarjan, M.D., chairperson, has not been able to move ahead with its plans for the project "Role of Education in the Peace Process" because of a lack of funds. Even though the project has received a \$40,000 challenge grant from the U.S. Institute of Peace, there have been no additional funds, so the project has not begun. The reason for this is twofold: the current situation in Israel does not encourage ongoing dialogue between Israelis and Arabs, although it is even more important than when the project began. In addition, the burden of responsibilities placed on our Office of International Affairs has not allowed adequate time for fund raising. Because of the support of the U.S. Institute of Peace, the task force still exists, but it is conceivable that this project could also be incorporated into the work of the proposed component on conflict resolution, if it is approved.

As to this proposed component on conflict resolution, the council believes that there are dangers in inappropriately applying psychiatric concepts to the understanding of and response to complex international conflicts. On the other hand, it also believes that there is a body of psychiatric knowledge and experience which is underutilized and can usefully contribute to such understanding and response. The object of such a task force would be to advise the APA leadership as to the best use of our psychiatric knowledge in addressing these issues and all activities leading up to such resolution. The focus of the work of the task force would be international, i.e., on conflicts between nations and subnations, and would build on the work done by other APA components, which have been or might be disbanded if this new project gets underway.

The council would like to point out that the next joint meeting cosponsored by APA will be held in 1990 in conjunction with the German Society of Psychiatry and Nervous Diseases. There have been preliminary meetings with Professor Hanns Hippus of Munich about various possibilities for time and location, and the planning will begin soon. In addition, invitations to cosponsor similar meetings have been received from England, Egypt, Israel, and Peru. APA guidelines indicate that these meetings can be held on an average of every 2 years, so it would be possible to schedule a meeting in an additional country in 1992. Which invitations to accept for 1992 and beyond is being discussed.

The Council on Medical Education and Career Development

Joel Yager, M.D., Chairperson

The primary responsibility of the council is to provide medical education to psychiatrists and other physicians. As part of this function, the council and its components provide recommendations to APA on psychiatric education for medical students, residents in psychiatry, and practicing psychiatrists. In addition, recruitment of high-quality medical students into psychiatry and the career development of psychiatrists are major functions of this council. The council comprises 18 components, each of which considers issues related to psychiatric education and career development.

1. *Proposed APA task force on disclosure.* The council recommended creation of an APA task force on disclosure last year. At its December 1987 meeting, the joint Reference Committee referred the recommendation back to the council for reconsideration and for holding until the AMA made its recommendations about licensure

confidentiality. In June 1988, the AMA House of Delegates approved a position statement concerning the confidentiality of a physician's personal medical record. The AMA position directly addresses the issue of disclosure of medical records for relicensure but leaves unresolved concerns about medical students, residents, and physicians in practice who may be stigmatized because they obtain psychiatric help. Components under the council will consider relevant issues and recommend what further steps APA should take to address these concerns.

2. *Guidelines from the Residency Review Committee for Psychiatry.* The council reviewed the Residency Review Committee guidelines for teaching transcultural psychiatry. The council discussed the problem of fitting additional curricular requirements into an already full four years of psychiatry residency training. The recommendation

is for the Committee on Graduate Education, together with representatives from the Council on National Affairs, to review the current wording of the Residency Review Committee guidelines to see whether it is adequate or needs modification. With respect to the *Special Requirements for Residency Training in Psychiatry* ("Essentials"), it was suggested that rather than specifying what ought to be included, the council might review the objectives of residency education. The more general question of access to and review of model curricula was discussed.

3. *Critical incidents study.* The council reviewed the critical incidents study performed for child psychiatry in the early 1970s by Dr. Jack McDermott, Ms. Christine McGuire, and their collaborators. In the child psychiatry study, a large number of child psychiatrists were each asked to record three incidents they had witnessed during the previous week that were examples of excellent or poor care given by child psychiatrists. The respondents were asked to provide information about what they had seen and why they viewed the incidents as particularly good or bad episodes of care. Altogether, 1,500 critical incidents were reported by several hundred child psychiatrists. The incidents were sorted to classify the care situations and cases of exemplary clinical competence. The process has had a significant influence on child psychiatry by helping to define the scope of clinical skills expected of residents in child psychiatry. The council agreed that a similar effort in general psychiatry is needed. To assess their interest in the project the following organizations were contacted: the American Psychiatric Association, American Association of Directors of Psychiatric Residency Training, Association for Academic Psychiatry, the American Academy of Child and Adolescent Psychiatry, American Board of Psychiatry and Neurology (ABPN), American College of Psychiatry (which administers the Psychiatry Residency In-Training Examination—PRITE), Residency Review Committee for Psychiatry, and the American Association of Chairmen of Departments of Psychiatry. A project proposal has been developed and entails a meeting of a planning group to prepare a project plan. After that meeting, foundation funding would be sought to carry out the 2–3-year project. The project would be a collaborative effort of psychiatric education organizations and housed in the APA Office of Education.

4. *Recertification in psychiatry.* The council reviewed the 1977 APA Position Statement on Recertification and the short history of recertification in psychiatry prepared by the Office of Education, which was based on the report of the Task Force on Recertification, chaired by Dr. Joseph Tupin. The council members discussed the external pressures for recertification, the position statement, the expected concerns of noncertified psychiatrists, and the current ABPN discussions of recertification. It was pointed out that the 1977 position statement, endorsing voluntary recertification, is currently operational and that reinstating a dialogue between APA and the ABPN would be helpful in developing APA recommendations. The consensus of the council was that external pressures for recertification are increasing. The council felt it was appropriate for APA to be proactive in recommending suitable voluntary recertification mechanisms for psychiatrists in order to forestall unacceptable externally imposed regulations. Clearly, anyone already certified by the ABPN has a lifetime credential and anyone who has never been certified through the ABPN cannot be recertified. Both concepts are well-established policies of the American Board of Medical Specialties. The council felt that several options should be available to psychiatrists interested in voluntary recertification. It was pointed out that research on the effectiveness of various recertification methods is still needed. The council recommended that the ABPN undertake such research.

The *Committee on Administrative Psychiatry*, Stephen L. Rachlin, M.D., chairperson, has selected Dr. Roger Peele to receive the 1989 Award in Administrative Psychiatry. The award is given at the APA annual meeting. The committee has surveyed existing administrative psychiatry fellowships. Of the 30 programs identified in the *Directory of Psychiatry Residency Training Programs*, only about half have responded to a questionnaire asking them to confirm the existence of their administrative psychiatry fellowships. Follow-up letters will be sent. The data will be supplied to the Task Force on Post-Residency Fellowship Training Programs. The oral portion of the administrative psychiatry certification examination was admin-

istered at Jewish General Hospital in Montreal on May 7, 1988. Seventeen candidates passed and are now certified in administrative psychiatry, five candidates failed, and five candidates received conditional passes that require re-examination in one or two topics. Of the 17 who passed, only four were successful the first time. The committee is concerned about the low number of candidates who pass both the written and oral examinations in one attempt.

The *Committee of Residents*, Henry Emmons, M.D., chairperson, discussed the AMA's June 1988 recommendations concerning legislative action on licensure confidentiality and expressed its opinion that APA should take the initiative in exploring related aspects of medical students' and residents' disclosures of past therapy. The committee discussed having a resident representative on the Residency Review Committee for Psychiatry. The Residency Review Committee is considering a 1-year trial of allowing a resident representative to attend its policy meetings but not its deliberations concerning accreditation of individual residency programs. The Committee of Residents is preparing recommendations on parental leave and time missed from training for APA to forward to the Residency Review Committee. Dr. Emmons plans to discuss coordination of APA resident activities with the leaders of the APA fellowship committees, the Board of Trustees member-in-training and member-in-training-elect, and the resident Assembly representatives.

The *Committee on Graduate Education*, Stefan Stein, M.D., chairperson, has been discussing parental leave and related pending federal legislation. The committee noted that current *Special Requirements for Residency Training in Psychiatry* and the Accreditation Council for Graduate Medical Education require a policy on parental leave. The policy may say that no leave is given, but it should be written and be available for all house staff entering the program. At the federal level, several Congressional committees have reported out bills that will mandate parental leave. The committee was asked by the Assembly to suggest strategies for reviewing and enhancing the requirements for classroom and clinical experiences involving transcultural psychiatry in psychiatry residency programs and the development of a model curriculum. The committee plans to work with the American Association of Directors of Psychiatric Residency Training in the compilation of published and reported cross-cultural curricula, and the APA Library will be the repository for the curricula. To reaffirm and endorse the need for a cross-cultural perspective in residency training programs, the committee asked APA to contact the Residency Review Committee for Psychiatry to review the requirements and evaluation of residency training programs. The committee discussed the implications of the current regulations in New York State regarding work hours for all residents in training. The committee met with the Committee on Gay, Lesbian, and Bisexual Issues about its proposed model curriculum and guidelines for instruction on gay, lesbian, and bisexual issues for residency training programs. As a result of the discussion, the council agreed to establish informal liaisons between that committee and two of its own components, the Committee on Graduate Education and the Committee on Medical Student Education. The Committee on Graduate Education met with the Council on Research to discuss developing research training tracks during residency training programs.

The *Committee on Consultation-Liaison Psychiatry and Primary Care Education*, Troy Thompson II, M.D., chairperson, reported on a joint meeting of leading national organizations in consultation-liaison psychiatry. Dr. Thompson has recently represented APA at meetings of the Association for Academic Psychiatry section on consultation-liaison, the Academy of Psychosomatic Medicine, the American Psychosomatic Society, and the Society of Liaison Psychiatry of New York. The committee also reported on progress in developing curricula in consultation-liaison aspects of AIDS, geriatrics, substance abuse, substance abuse during pregnancy, and AIDS and pregnancy. The committee recommended that five individuals who have served informally as liaisons to various organizations be appointed as official liaisons. The committee discussed changing its name and charge because of concerns about the term "behavioral medicine." The committee felt that it was wise to include behavioral medicine in the committee charge because an increasing number of psychiatrists are involved nationally with behavioral medicine societies and in many medical schools the division of behavioral medi-

cine is not part of a consultation-liaison psychiatry service and is not headed by psychiatrists. It was felt that to ignore this important field would be to limit psychiatrists' opportunities to work with internists and other primary care physicians who have demonstrated a strong interest in behavioral medicine.

The *Committee on the Impaired Physician*, Robert McDermott, M.D., chairperson, is revising the information packet concerning impaired physician programs that is sent by the Office of Education in response to inquiries and is revising the guidelines on medical student impairment and will review them at the committee meeting in May 1989. Members of the committee have been very active in planning the upcoming AMA conference on impaired physicians. Dr. James Lurie and Dr. Michael Myers have prepared a videotape on interviewing impaired physicians. If the videotape is well received, the committee hopes to develop additional videotapes on medical student stress reduction and/or impairment. The committee also continues to review the guidelines for the care and management of physicians who get AIDS.

The *Committee on Independent Study*, Keith Johansen, M.D., chairperson, has two new projects. One is the development of a *DSM-III-R* modular workbook in conjunction with the Task Force on Educational Activities for *DSM-III-R*. The APA Office of Education staff is assisting in developing the first module as a pilot to assess the feasibility of the project. The second project is development of a series of publishable reports for APA members on computer technology: how to use computers, overcoming computer phobia, and special topics of concern to psychiatrists using computers.

The *Committee of Young Psychiatrists*, David Whitehouse, M.D., chairperson, met for the first time in September 1988. Dr. Fink appointed Dr. Whitehouse as delegate and Mary Ellen Foti as alternate delegate to the AMA Section on Young Physicians. Committee members were concerned that only a few of them would be able to attend the APA annual meeting; young psychiatrists who become junior members of joint practices must provide coverage for colleagues during the annual meeting. The committee felt that the young psychiatrists who attend the annual meeting will need an opportunity to foster development of this new component. The committee will sponsor a reception for all young psychiatrists at the 1989 annual meeting. It will also collect data on the demographic characteristics and distribution of young psychiatrists and will prepare an article to alert young APA members about the committee's existence and intentions.

The *Committee on Medical Student Education*, Leah Dickstein, M.D., chairperson, has discussed extensively the value of recruiting medical students to be members of APA. The representative of the American Medical Student Association pointed out that approximately 70% of all APA Medical Student members become APA Members-in-Training. The committee feels that the additional recruitment of student members, particularly at the 3rd-year level, after their psychiatric clerkships, would be most effective. As part of a recruitment strategy, brochures will be sent to 127 medical school departments of psychiatry for the approximately 16,000 students. The committee has recommended the creation of the Nancy C.A. Roeske Certificate of Recognition for Excellence in Medical Student Education, which is tentatively scheduled to be presented for the first time in 1990. The committee plans to designate a "Medical Student Day" at the APA annual meeting to encourage medical student attendance.

The *Task Force to Facilitate Communication Between APA and the ABPN*, Richard Shader, M.D., endorsed the working recommendations of the Task Force on Recertification for voluntary recertification and recommended that APA take a proactive role in helping the approximately 8,000 noncertified psychiatrists to become certified by the ABPN or the Royal College of Psychiatrists of Canada. The task force also recommended that APA publicize the four openings for ABPN Directors during the next 2 years, two beginning in 1990 and two in 1991, and that it notify all potentially interested APA components. The ABPN makes the appointments from among two candidates recommended by the APA and two recommended by the AMA with advice from APA. The task force noted that the ABPN has sent a letter of intention to the American Board of Medical Specialties about its plan to proceed with certification for added

qualifications in geriatric psychiatry. The task force recommended that APA communicate with the ABPN about including requirements for appropriate exposure to experiences in internal medicine and neurology for candidates who will take the examination for added qualifications in geriatric psychiatry. A recent report of the Association of American Medical Colleges indicated a decrease in the relative number of minorities entering medical school (i.e., the same number but a lower proportion of medical students), which is a major concern in the recruitment of minorities to medicine and psychiatry. The task force urged APA to do all it can to sustain minority recruitment. The task force reviewed the draft report of the Council on Graduate Medical Education and endorsed the concern about the shortage of psychiatrists and the suggested role of foreign medical graduates in addressing this shortage.

The *Task Force on Educational Activities for DSM-III-R*, Michael Fauman, M.D., chairperson, will work with the Task Force on *DSM-IV*, under the Council on Research, to conduct a survey on the educational problems psychiatrists have had in using *DSM-III-R*. The task force is preparing a discussion guide based on 50–75 video vignettes being produced at Mt. Sinai Hospital in Detroit. The written discussion leader's guide, with the verbatim clinical material, can be used for teaching *DSM-III-R* and, with minor modifications, should be useful for teaching *DSM-IV*. The council will develop a procedure for reviewing the guidebook to assure quality and educational value.

The *Committee on Continuing Education*, John Goethe, M.D., chairperson, was working on a comprehensive listing of APA-sponsored programs. Due to the variety and complexity of the APA programs offered as part of the annual meeting, H&CP Institute, and other continuing education activities, the committee opted not to continue developing the list. The committee will instead develop a contemporary concept of continuing medical education for psychiatrists and a statement of the expectations for the future directions of continuing education, especially the latest educational technology and the role of lifelong learning.

The *Task Force on Post-Residency Fellowship Programs*, George Pollock, M.D., chairperson, will prepare a survey of fellowship programs in all psychiatric subspecialties as part of a database on psychiatry fellowship training. The task force will also compile a list of criteria to define fellowship training and recommend policy and procedures for accrediting fellowship programs.

The *Selection/Advisory Committee, Minority Fellowship Program*, Charles Pinderhughes, M.D., chairperson, reported that out of 10 nominees, eight new fellows were chosen for 1988–1989. In addition, the committee approved the continuation of four fellows as trainee-consultants. The committee reviewed its name and charge this year and has proposed that they be revised to better reflect its current activities. The proposed new name is the "APA/NIMH Minority Fellowship Program." Last year the committee obtained approval to seek funding from sources other than the National Institute of Mental Health (NIMH), and it has made a request to the Upjohn Company.

The *Committee on Psychiatrist Leadership in Public Mental Health Programs*, Robert Leon, M.D., chairperson, has developed standards and guidelines for chief executive officers and medical directors of public health facilities. The committee has also discussed the recommendation that state departments of mental health help finance the training of psychiatrists for administration in the public sector. The committee recommends that NIMH fund a program for administrative psychiatry training which would require the development of links between states and university medical schools and matching funds from state mental health systems. The committee has also recently reviewed the study of psychiatrists in state systems from the National Association of State Mental Health Program Directors.

The *Steering Committee, Psychiatric Knowledge and Skills Self-Assessment Program VI (PKSAP VI)*, Gordon Strauss, M.D., chairperson, reported that the third study unit of PKSAP (module A) was mailed to subscribers in June 1988. Because of errors by the mailing house, the staff of the Office of Education and American Psychiatric Press had to respond to numerous inquiries. PKSAP VI became available in January 1988, and the income in the first 9 months was \$370,325. This amount is larger than the revenue from PKSAP V

during the same period of its first year (1982). Module B will be available by mid-January 1989.

The *APA/Mead Johnson Fellowship Selection Committee*, James Barter, M.D., chairperson, reported that out of 52 nominees, 15 new fellows and one alternate were selected this year. Starting in 1989, Mead Johnson will issue a block grant to fund this program. In 1988 fellows participated as teaching faculty at the H&CP Institute for the

second time, and this opportunity has now been made a part of the fellowship program.

The *APA/Burroughs Wellcome Fellowship Selection and Program Committee*, Roger Peele, M.D., chairperson, reported that 48 nominees were reviewed for the 1988–1990 program and 10 new fellows were selected. The Board of Trustees approved new guidelines for evaluating psychiatry residents for this fellowship program.

The Council on National Affairs

Lindbergh S. Sata, M.D., Chairperson

This council is responsible for matters of national interest to psychiatry and the patients it serves. Social and health-related issues that affect underrepresented groups in the general population and within the profession warrant particular attention by this council. To address these issues, the council works closely with representatives from the Assembly, APA staff, and relevant APA components while overseeing and assisting the 13 components reporting to the council.

In May 1987 the Assembly passed an action paper asking APA to develop a cross-cultural curriculum to be used by the Residency Review Committee for Psychiatry in evaluating residency training programs for accreditation. The council was asked to discuss the curriculum at its September meeting, at which time it asked its minority committees to prepare curriculum proposals (bibliography, outline of issues, curriculum). The council is working closely with the Committee on Graduate Education and APA's Office of Education on the disposition of these curriculum proposals. The committee and the Office of Education are working with the Curriculum Committee of the American Association of Directors of Psychiatric Residency Training to prepare an annotated bibliography, which will be made available to residency training directors. The annotation will make clear that the complete curriculum is available from the APA library. Dr. Philip Bashook of the APA Department of Education is collecting these proposals and will work with the APA librarian to catalogue these bibliographical entries and curricula.

Acting on a request from Dr. Paul Fink, the council discussed the report of the Ad Hoc Committee on Liaison Activities. Dr. Pedro Ruiz was the primary reviewer. All the council members especially stressed the importance of joint meetings with other organizations during the annual meeting, whether they are business or social gatherings.

At the request of Dr. James Trench, the council reviewed a paper from the Ad Hoc Committee on Subspecialization and paid particular attention to criteria by which additional groups might be measured and the mechanisms in the APA governance system to handle these requests. Dr. James Thompson was the primary reviewer. Some council members asked if this ad hoc committee has examined the criteria of other subspecialties and suggested that it do so.

In response to a letter from Dr. Chester Schmidt, chairperson of the Work Group on Codes and Reimbursement, the council discussed the list of procedural terms drawn up by the work group. Dr. David Briones was the primary reviewer.

On July 7, 1988, Dr. James Thompson testified on behalf of the Association of American Indian Physicians at a Congressional oversight hearing on community-based mental health initiatives for American Indians and Alaska natives. Dr. Linda Cross testified on behalf of APA. Both Drs. Cross and Thompson were distressed by a suggestion from a representative from the American Psychological Association that, in view of the scarcity of qualified health care personnel, psychologists in the Indian Health Service be allowed to prescribe psychotropic medication. Dr. Thompson pointed out that

other government programs with reimbursement services should note that this proposal affects populations they serve.

Dr. Paul Fink asked the council to review a letter and proposed position statement from Dr. Joseph Westermeyer on mental health care for refugees. The council and four of its committees (Asian-American, Black, and Hispanic Psychiatrists and Foreign Medical Graduates) agreed in principle with the proposed position statement. In a subsequent conversation between Drs. Sata and Westermeyer, the latter said he was going to revise the statement and would submit the revision for consideration by APA.

The council reviewed the article "National Initiatives for Care of the Medically Needy" in response to a memo from Dr. John Hamilton. The council felt that the action item approved by the joint Reference Committee, the Assembly, and the Board was sufficient and that what was needed was follow-up. The action item was for the Board of Trustees to urge APA members to donate 5% of their clinical practice time to the provision of voluntary, nonreimbursed care to members of minority and underrepresented groups, including women, children, patients with diseases related to the human immunodeficiency virus (HIV), and the poor. The council voted to ask the joint Reference Committee to recommend that the Board of Trustees emphasize such service to the APA membership.

The *Committee on Abuse and Misuse of Psychiatry in the U.S.*, Roger Dale Walker, M.D., and Jose M. Pena, M.D., cochairpersons, discussed the first draft of the position paper "Abuse and Misuse of Psychiatry in the U.S.: The Need for an Institutional Ethic" and decided to revise it in light of the comments made by committee members. The committee will submit the final draft to the council and will recommend that the council ask the following components to review the paper: Ethics Committee, Task Force on Professional Practice Issues in Organized/Managed Care Settings, Committee on Quality Assurance, Committee on Graduate Education, and Task Force on Use and Misuse of Psychiatric Diagnoses in the Courts.

The committee reviewed cases and letters it received and decided which courses of action to take.

At the conference of the Association of American Indian Physicians in California, the *Committee of American Indian/Alaskan Native Psychiatrists*, Linda Cross, M.D., chairperson, continued its efforts to recruit more American Indian medical students into psychiatry. It also agreed to contribute a chapter on American Indian identity issues for a book being prepared by the Association of Native American Medical Students. This book is aimed at American Indian students who are considering college and medical school.

Besides recruitment, the committee discussed the retention of American Indian college and medical students and the factors that affect their retention and attrition. Dr. Cross is considering research on this topic now that she is on the faculty of Michigan State University.

As mentioned earlier in this report, Dr. Cross testified on behalf of APA at the July 7, 1988, Congressional oversight hearing on com-

munity-based mental health initiatives for American Indians and Alaska natives. One of the concerns brought up then was the lack of coordination between alcoholism and mental health treatment in many communities. Dr. W. Craig Vanderwagen of the Division of Clinical and Preventive Services in the Indian Health Service was also at the hearing and asked for suggestions on how to improve such coordination. He accepted this committee's invitation to attend its September meeting, as did Mike Mahsetky (Office of Legislation, Indian Health Service), Patricia Zell and Yvette Joseph (legislative aides to Senator Inouye), and Bill Richards (member of the APA Committee on Alcoholism and director of Mental Health and Alcoholism Services, Indian Health Service, Alaska).

As also mentioned earlier in this report, the committee was perturbed by the suggestion that psychologists in the Indian Health Service be allowed to prescribe psychotropic medicine. The committee feels that if this happens, it could affect the patient's safety. The committee instead supports providing continuing medical education to primary care physicians in the Indian Health Service so that they can learn more about prescribing psychotropic medication.

The *Committee of Asian-American Psychiatrists*, Joyce S. Kobayashi, M.D., chairperson, held a lively discussion of whether it was appropriate for the committee to indicate its enthusiasm for *The Mental Health of Korean Americans: Resource Book*, a proposed text for the Asian-American mental health research literature. Not having seen the draft, the committee was unable to evaluate the scientific merits of the book but wished to convey its support for the book's publication.

Dr. Norma Panahon is spearheading the fund raising for the revised edition of the *Directory of Asian-American Psychiatrists*. Some committee members brought lists of private foundations that might be tapped for funds for the Asian-American Mental Health Award. Dr. Grant Ko is the informal liaison to the Scientific Program Committee on this award.

With regard to the cross-cultural curriculum proposal requested by the council, the committee decided to submit "Asian and Pacific American Patient Issues in Psychiatric Residency Training Programs," which is a chapter in *Mental Health & People of Color: Curriculum Development and Change*.

The committee spent many hours discussing the organization of the 1989 symposium on mental health research in Asia, which is being cosponsored by the Pacific Rim College of Psychiatrists. The participating countries include Japan, Korea, Taiwan, the Philippines, India, Hong Kong, and the United States. During a plenary session in the morning a primary lecturer from each country will present the status of research on schizophrenia, affective disorders, and anxiety disorders. A small group of representatives from all countries will take part in an afternoon work group. This will be followed by a plenary session to summarize the recommendations for future collaborative research.

The *Committee of Black Psychiatrists*, Ernest A. Kendrick, M.D., chairperson, discussed mental health issues that have received little attention from organized groups and may disproportionately affect blacks. These issues include victimization (rape, witnessing rape, homicide, witnessing violence), multi-infarct dementia, poststroke depression, and a high death rate.

Dr. Delores Parron, Associate Director for Special Populations at the National Institute of Mental Health (NIMH), reviewed new NIMH service and personnel policies and issues and their effects on blacks. She also said that NIMH would announce a minority fellowship program in psychiatry aimed at medical students and residents. This will consist of one award to either an institution or association.

The committee noted that although the acquired immune deficiency syndrome (AIDS) affects blacks disproportionately, there are no black psychiatrists on either of APA's AIDS components. However, several black psychiatrists engaged in AIDS research were invited as observers to the July meeting of the Committee on Psychiatric Aspects of AIDS.

The committee discussed two actions taken by the AMA House of Delegates: Report P of the AMA Board of Trustees, which involves physician manpower, and Resolution 180, "Minority Students and Faculty in U.S. Medical Schools." The committee and council voted to ask the joint Reference Committee to recommend that the Board

of Trustees authorize the Medical Director to write to the AMA to say that APA applauds AMA's sensitivity to minority manpower issues, that APA is a significant medical specialty with an active interest in both of these AMA actions, and that APA is willing to help AMA increase the number of minority physicians, students, and faculty. Dr. Sata discussed this action with Dr. John McGrath, who concurred that this was a diplomatic way of ensuring APA involvement.

The *Committee on Foreign Medical Graduates*, Walter Weintraub, M.D., chairperson, discussed the difficulties often faced by psychiatric residency training directors in evaluating the credentials of applicants who are graduates of foreign medical schools. Unlike graduates of American medical schools, most foreign medical graduates (FMGs) have no records of achievement in examinations testing knowledge of the behavioral sciences and psychiatry. The examination required of FMGs for certification by the Educational Commission for FMGs contains questions in the behavioral sciences and psychiatry, but an FMG's performance on this part of the test is not reported as a separate score. The committee decided to request the Educational Commission for FMGs to calculate FMG behavioral science and psychiatry scores and to make them available to psychiatry training directors, with the permission of the FMG applicants.

The committee also discussed licensure. Licensed foreign medical graduates face discriminatory practices when trying to obtain licenses in certain states through reciprocity. No matter how many state board examinations they may have passed, no matter what their accomplishments, FMGs may be required to meet more stringent reciprocity standards than graduates of American medical schools. Recently bills have been introduced in Congress to try to correct this situation. The committee asked the council to urge APA to support H.R. 3241, which would "prohibit a state from subjecting a foreign medical graduate (FMG), who has completed residency training in the U.S. and who has obtained a license to practice medicine in any state, to any condition or requirement that materially differs from those applied to graduates of U.S. medical schools. States that violate this prohibition would lose their eligibility to receive Medicaid payments."

APA's statement on FMGs before the Subcommittee on Foreign Medical Graduates of the Council on Graduate Medical Education of the U.S. Department of Health and Human Services supports the principles of nondiscrimination contained in the aforementioned bills. The AMA has argued that licensure is a state function, and APA will continue to work with the AMA and will review the results of the Government Accounting Office study on the extent of discrimination against FMGs in licensing to see if the results clearly detail the extent and amount of such discrimination. The council shares the committee's concern and will work with the Division on Government Relations on this matter.

On Sept. 9, 1988, Dr. Robert Volle, President of the National Board of Medical Examiners, met with the committee and promised to consider a request by the Educational Commission for FMGs (should one be made) that FMGs' scores on the Foreign Medical Graduate Examination in the Medical Sciences be reported in the same manner as the results of the examinations of the American Board of Psychiatry and Neurology (ABPN).

Dr. Samuel Asper, President Emeritus of the Educational Commission for FMGs and consultant to the committee, discussed commission-sponsored international medical programs and projects. He presented to the committee a new publication, the *1988 Directory of International Programs and Projects of U.S. Schools of Medicine, Dentistry, Pharmacy and Public Health*.

Dr. Weintraub talked about the *1988 Directory of Foreign Medical Schools*, which describes all medical schools that may be of interest to U.S. citizens who want a medical education abroad.

Dr. Stephen Scheiber, Executive Secretary of the ABPN, described the various components of the psychiatry Board examination, answered questions about the treatment of FMGs by examiners, and discussed the ABPN's plans for subspecialization examinations.

The committee spent considerable time discussing the increase in criticism of FMGs, which seems to stem from the perceived glut of American physicians. The committee was pleased with Dr. Fink's editorial on this issue in *Psychiatric News*.

James P. Krajewski, M.D., chairperson of the *Committee on Gay, Lesbian, and Bisexual Issues*, reported on his meeting with the Com-

mittee on Advertisers and Exhibitors. He had recommended that the military be prohibited from recruiting at the annual meeting because its hiring practices discriminate against gay men and lesbians. The Council on Internal Organization also discussed this matter and recommended "that organizations that discriminate in recruitment or employment on the basis of gender, race, religion, or sexual orientation be prohibited from recruiting or offering employment in APA exhibition areas." The committee concurred with this statement and asked the council to support this action item from the Council on Internal Organization. The council voted to do so and, in the event that the statement is substantially altered, to ask the joint Reference Committee to approve the council's original statement instead.

In a letter to Dr. Carol Nadelson, Dr. Krajewski pointed out what he felt was a major problem with the section on homosexuality in the *Textbook of Psychiatry*, which was published by the American Psychiatric Press, Inc. (APPI). Dr. Krajewski has since received a letter from Dr. Nadelson and a telephone call from Dr. Talbott, both of whom expressed their desire to resolve any problems.

With regard to *DSM-IV*, the committee felt that it was very important for its members to have a chance to review or comment on any issues in *DSM-IV* that related in any manner to sexual orientation, sexuality, or gender identity. It decided to write to Dr. Allen Frances indicating this wish. It also decided not to make any recommendations on diagnoses related to homophobia or other kinds of conditions or situations.

The *Committee of Hispanic Psychiatrists*, Eduardo R. Val, M.D., chairperson, discussed ways to recruit more Hispanic psychiatrists for the Caucus of Hispanic Psychiatrists at the annual meeting. One recommendation was to ask *Psychiatric News* to publicize the caucus. Another was to use the forthcoming *Biographical Directory* to compile a list of Hispanic psychiatrists and to urge them to join the caucus.

Dr. Luz Guevara-Ramos translated information on AIDS into Spanish in response to a request from the then Task Force on the Psychiatric Aspects of AIDS. The translation was passed on to the task force, which is now a commission.

The committee felt that a series of brochures on drug abuse and other topics that will be available during Mental Illness Awareness Week should also be available in Spanish. The committee broached the subject with the Division of Public Affairs, which will consider it. The committee would provide a Spanish translation of the series.

During a meeting with Dr. Allen Frances concerning *DSM-IV*, it was agreed that the committee will nominate advisors to the subgroups on diagnostic categories. These advisors will be experts in the respective categories and will be Hispanics or familiar with the impact of these categories on Hispanics.

The *Committee on Occupational Psychiatry*, Duane Q. Hagen, M.D., chairperson, asked Dr. Jean Hamilton to draft a position statement on sexual harassment and other forms of gender-based employment discrimination, which Dr. Hagen presented to the Council on National Affairs in May. The statement was revised and approved by the joint Reference Committee, passed by the Board of Trustees, and published in the November 1988 issue of the *Journal*.

Dr. Peter Boxer analyzed the responses to a questionnaire sent to psychiatrists involved or interested in occupational psychiatry. Those working in occupational psychiatry indicated a desire for more workshops, a newsletter, and help in gaining entry to organizations. The respondents reported a wide range of activities in occupational psychiatry, such as consultation to organizational units and evaluation of stress-related disability.

With regard to stress-related disability, Dr. Moss indicated that it was becoming a major issue at one of the companies with whom he consults. He feels that the role of the psychiatrist is 1) to advise a company on how, internally, it can prevent stress in its employees and 2) to help with the definition of impairment and with evaluation of cases.

The committee approved the final version of its employee assistance paper and voted to forward it to the council. The committee thanked Ms. Elyse Zukerman for her excellent work in organizing and editing the material. The council, which had received a copy of the paper before coming to Washington, discussed it and voted to ask the joint Reference Committee to recommend that the Board of Trustees approve the publication of the paper "Employee Assistance Programs and the Role of the Psychiatrist" as a committee report.

For the 1989 annual meeting the committee is planning a component workshop, a committee meeting that will be open to interested parties, and a coffee reception for around 150, for which the committee will seek outside funding. The council voted to ask the joint Reference Committee to request the Board of Trustees to authorize the committee to seek \$1,000 in outside funds for the coffee reception.

The *Committee on Psychological Aspects of Nuclear Issues*, Judith Lipton, M.D., chairperson, discussed its proposal for a symposium at the 1989 annual meeting and the difficulty of getting speakers who are not APA members because of the cost entailed.

During a discussion of its role, the committee decided, after much debate, not to submit a policy statement on the psychological impossibility of rational triage in the event of a nuclear war. The committee also decided to examine the psychiatric and psychological aspects of national security, a 3–5-year project. Messrs. Samuel Lewis and Joseph Montville will be invited to the committee meeting in September 1989.

The *Committee on the Psychiatric Aspects of AIDS*, Stuart E. Nichols, Jr., M.D., chairperson, held a special meeting on July 30 and 31, 1988, during which it approved the dissolution of this committee and the Ad Hoc Committee on AIDS Policy and the establishment of a Commission on AIDS and an Office of AIDS in their stead. This recommendation was presented by Dr. Robert Pasnau to the Board of Trustees on Sept. 10, 1987. The Board approved the recommendation.

Dr. Nichols thanked the council for its support and, in particular, Dr. Pedro Ruiz, whose unflagging efforts on behalf of this committee made it possible for an informal subcommittee to progress to a task force, a committee, and, finally, a commission.

The *Committee on Religion and Psychiatry*, Marc Galanter, M.D., chairperson, received encouraging comments from the Ethics Committee and is waiting to hear from the Assembly regarding the proposed "Guidelines on Conflict Between Religious or Ideologic Commitment and Psychiatric Practice." These comments will help this committee to decide on its next course of action.

The committee selected William Meissner, M.D., for the 1989 Oskar Pfister Award.

The *Committee on Women*, Nada L. Stotland, M.D., chairperson, was represented by Dr. Peggy Stephens at the meeting of the Membership Committee, during which it was agreed that both committees would place even more emphasis on addressing the needs of female members in training and on recruiting women into organized psychiatry. Dr. Rodrigo Munoz pointed out that disproportionate numbers of female members ask for waivers and drop out of APA.

The committee believes that *DSM-IV* should distinguish and address gender-related and non-gender-related etiologic issues and their role in prevention and treatment.

The committee spent considerable time discussing the genesis and timing of the request for a curriculum proposal. The request originated from the Assembly and was relayed to the Council on National Affairs, which then asked for a curriculum on women. However, the committee members responsible for drafting the curriculum and its informal consultant felt that "gender curriculum" was a more appropriate term. The members who drafted the curriculum expressed their wish that it receive the imprimatur of the Board of Trustees and that it be incorporated into the testing procedures of the ABPN. The ultimate goal of the curriculum is the integration of this information and approach into all aspects of residency training.

Phyllis Greenberger of APA's Division of Government Relations met with the committee and discussed the Family Leave Act and the Child Care Act proposed in Congress. The latter has bipartisan support because of the growing number of working mothers.

The committee has corresponded with Dr. Irving Schneider, who raised the issue of nonsexist language. Dr. Debbie Carter has corresponded with the editors of various APA publications, of whom only Dr. Talbott responded. He indicated that while there is no specific admonition about gender-neutral language in *Hospital & Community Psychiatry*, the "Instructions for Authors" encourages them to use gender-neutral language. The committee will suggest to the editorial boards of the APA publications that gender, ethnic, and racial bias be eliminated from the language of the publications and that caveats be included in the formal instructions to authors and editors.

The Council on Psychiatric Services

J. Frank James, M.D., Chairperson

As a focal point for many APA service issues, the council and its components have proactively pursued difficult and controversial topics that should contribute to the Association and its members. The range of issues involving private practice, public service, managed care, and specialized care provides this council with an excellent perspective to share with the joint Reference Committee, Assembly, and Board of Trustees.

Many issues, in fact, need to be considered by more than one component of the council. For this reason and to render the number of components more manageable, the council was organized into five groups, and liaison members of the council coordinate overlapping concerns. This organization has improved communication and facilitated the council's work.

The *Committee on Federal Government Health Services*, William B. Hunter, M.D., chairperson, was established in 1966 to provide information and advice concerning any psychiatric affairs of the federal government health services, particularly the Army, Navy, Air Force, and Veterans Administration. The committee also has attended to matters of the Federal Bureau of Prisons, the Indian Health Service, and the U.S. State Department. With the more recent establishment of the Joint Commission on Government Relations, the Committee on Psychiatric Services in the Military, and the Committee on Veterans Administration Affairs, many of the major functions of the Committee on Federal Government Health Services have been redirected to the new components. In December 1988 the Board of Trustees disbanded this committee. To ensure that certain interests do not go untended, monitoring of the psychiatric interests of the following agencies has been assigned to other APA components: Indian Health Service (Committee of American Indian/Alaskan Native Psychiatrists), State Department (Council on International Affairs), and Bureau of Prisons (Council on Psychiatric Services). The council wishes to express its appreciation to Dr. Hunter and the members of the Committee on Federal Government Health Services for their excellent efforts over the years.

The *Committee on Alcoholism*, Richard Frances, M.D., chairperson, has focused on the growing interest in designating alcoholism, drug abuse, and other addictions as a subspecialization area. It met with members of APA's Ad Hoc Committee on Subspecialization to discuss APA's process of determining whether a field qualifies as a subspecialty and what pathways are available for formal recognition of a subspecialty. The committee, with the Committee on Drug Abuse, pointed out that the population of patients with drug and alcohol abuse is large and is seen in private offices, hospitals, mental health facilities in both public and private systems, jails, and job-related outpatient settings. Psychiatrists treating such patients work in all types of settings. The committee believes that the patient population affected by drug and alcohol abuse is sufficient to warrant greater study and action within APA than can be provided by two components. At the committee's recommendation, in the coming year the council will bring before the joint Reference Committee and Board a proposal for establishing a council on addictive disorders.

The *Committee on Drug Abuse*, Edward Kaufman, M.D., chairperson, is concerned about the requirement by certain states that applicants for licensure disclose their psychiatric or drug abuse treatment histories. The committee is particularly concerned about the lack of confidentiality of this information in some states and the effect such requirements have on individuals' decisions to enter therapy. The committee is joining the Committee of Residents and the Council on Medical Education and Career Development in studying the problem.

In concert with the Committee on Alcoholism, the committee has reiterated its request that APA ensure that drug and alcohol abuse are specifically included in public statements endorsed by APA and

that drug and alcohol abuse are associated with psychiatry in APA public affairs and government relations efforts.

The *Committee on Rehabilitation*, Arthur Meyerson, M.D., chairperson, has actively supported liaison with other organizations and agencies to promote psychiatric rehabilitation in a variety of programs. Specifically, the committee has representatives on the President's Committee on Employment of the Handicapped and the Mental Health Advisory Group to the Commission of the Rehabilitation Services Administration. The committee has encouraged greater liaison with the Social Security Administration through links with its new medical director, continuing cosponsorship of a program during the APA annual meeting, and other available opportunities. In concert with the Task Force on Social Security Income/Social Security Disability Insurance, the committee plans to explore a consensus conference on disability issues with the Social Security Administration and several other groups.

The *Committee on State Mental Health Systems*, Ernest Klatte, M.D., chairperson, focused its energy on encouraging psychiatrists to become active in local planning efforts to ensure adequate services for the severely mentally ill. Last fall it called attention to the fact that the states were completing plans to obtain additional federal funding for psychiatric services. While the committee supports the development of community-based services, its major concern was the need for states to ensure adequate inpatient services and resources for the severely mentally ill. To that end, the Assembly agreed to encourage members and district branches to become involved in state planning, and letters were sent to the district branch presidents. The committee also encouraged publication of various informational articles to help psychiatrists who are involved in local planning. The committee continues to meet with representatives of the National Association of State Mental Health Program Directors and others with special interests in this area.

The *Committee on Liaison With the American Hospital Association*, Mark Gould, chairperson, meets with its counterpart committee from the American Hospital Association (AHA) twice a year. In the past year, the joint AHA/APA committee has renewed its commitment to seeing that each organization keeps the other informed of activities of mutual interest. The joint committee has examined and identified several areas where additional collaboration would be helpful. One result is the joint exploration by the quality assurance departments of the two organizations of whether they might launch joint efforts to improve the efficiency and effectiveness of quality assurance procedures in hospitals. The APA committee asked the council to give it more specific guidance as to issues it would like explored with the American Hospital Association.

The *Committee to Coordinate the Functions of H&CP Journal, Service, and Institute*, H. Richard Lamb, M.D., chairperson, directed its energy toward expanding the membership of the Hospital & Community Psychiatry Service and enhancing its programs. The Service's membership of 780 institutional members was increased by about 45 members this year as a result of new contracts with corporate hospitals. The Psychiatric Placement Service, which assists psychiatric facilities in recruiting psychiatrists and is a part of the Hospital & Community Psychiatry Service, had a successful year. The council hopes that APA members will take advantage of this low-cost service.

The *Institute on Hospital & Community Psychiatry Program Committee*, Stuart Keill, M.D., chairperson, planned and executed the successful 1988 Institute on Hospital & Community Psychiatry, which was held in October in New Orleans. The Institute had the highest attendance and largest scientific program ever, with more than 180 scientific sessions. Numerous affiliated organizations held meetings in conjunction with the Institute. The next Institute is scheduled for Oct. 15-19, 1989, in Philadelphia.

The *Committee on the Chronically Mentally Ill*, David Cutler, chairperson, has continued its tradition of offering many educational opportunities during the APA annual meeting for psychiatrists to increase their knowledge about treatment of the chronically mentally ill. Several scientific offerings on the 1988 program and proposed for 1989 were suggested by committee members. Several members of the committee worked with representatives of other organizations that focus on psychiatric treatment, training, and the needs of the chronically mentally ill to develop a basic residency curriculum concerning the chronically mentally ill. The authors hope to publish their report and persuade colleagues to attend to the needs of this population; the council recommended the report for APA endorsement.

The committee will communicate to Assembly officials suggestions for how the district branches might develop local committees on the chronically mentally ill, liaisons with local citizen groups, government planning groups, etc. They have also urged the district branch legislative groups to pay particular attention to matters affecting the care of the chronically mentally ill.

The *Committee on Private Practice*, Boris Rifkin, M.D., chairperson, made specific recommendations to increase the involvement of private practitioners in APA components and offices. As a result, in December 1988 the APA Board of Trustees called for more frequent consideration of private practitioners in the active APA membership for appointments to components and councils and for nominations for office. The committee also pointed out the financial hardship suffered by private practitioners who are elected to office and must donate considerable amounts of time to APA service. The council recognized the commitment, and sometimes sacrifice, that private practitioners make to serve in busy APA posts but also recognized that this applies, in varying degrees, to all members. It recommended that APA review possible mechanisms for enabling individuals to serve in these roles, regardless of professional affiliations or background. This recommendation was referred to the Nominating Committee and Budget Committee for study.

The committee continues to sponsor a full day of private practice workshops during APA's annual meeting and hosts an annual round table of private practice representatives from the district branches.

The *Committee on Psychiatric Services in the Military*, Leonora Petty, M.D., chairperson, has maintained contact with the newly established Society for Military Psychiatrists. While this society is separate from APA, it is hoped that the two organizations can collaborate on mutual concerns. The committee also brought to APA's attention issues in graduate medical education in the military, reduction in time for direct clinical care, a pilot project within the Army to determine the effects on quality of care of granting psychologists credentials to prescribe psychoactive drugs, and the development of diagnosis-related groups for use in the Army.

The *Committee on Veterans Administration Affairs*, Fred Gugenheim, M.D., chairperson, was established in March 1988 and held its first meeting in September. It wasted no time in encouraging APA to positively influence the Veterans Administration (VA) in recruitment and retention of staff, development of mental illness research and education centers, establishment of an office on mental illness research within the VA central office, adjustments to the statistical base used to determine the number of available psychiatry residency openings, and ongoing efforts to increase applicable budgets through legislation.

The *Committee on the Practice of Psychotherapy*, Marcia Goin, M.D., chairperson, continued to develop the document with the working title "The Role of Psychotherapy in Psychiatric Treatment." It hopes that this document will serve as a basis for several

shorter documents addressing specific audiences. The committee presented "Three Psychotherapy Approaches to the Treatment of Depression" as part of its educational focus during the 1988 annual meeting.

The *Task Force on Professional Practice Issues in Organized/Managed Care Settings*, Haroutun Babigian, M.D., chairperson, submitted draft guidelines for psychiatric practice in community mental health settings. The guidelines are sensitive to the balance of expectations, responsibility, and authority that psychiatrists in these settings must achieve to ensure quality care. The guidelines were approved by the Board of Trustees in December 1988. The task force is also drafting guidelines for psychiatric practice in staff model health maintenance organizations.

The *Task Force on Psychiatric Services for Mentally Retarded/Developmentally Disabled Adults*, Ludwik Szymanski, M.D., chairperson, is beginning its development of recommendations on ways psychiatrists might be more accessible for treatment of this population.

The *Task Force on Clinician Safety*, William Dubin, M.D., chairperson, is addressing the incidence of assault on psychiatrists. It proposes to gather information about the events preceding such incidents and their effects by interviewing a number of psychiatrists who have been assaulted. The committee will participate in a symposium on clinician safety and sponsor a workshop on the topic at the 1989 annual meeting. Other aspects to be addressed are how to handle repeated threats, useful office design features, and safety and security measures. The task force will also contact the Committee of Residents to see if there are training programs that carefully address clinician safety.

The *Task Force on Psychiatric Services in Jails and Prisons*, Henry Weinstein, M.D., chairperson, completed work on a position statement concerning services in these settings, which was approved by the Board and Assembly. The task force also submitted for review a report that contains principles and guidelines for services in jails and prisons. The document will undergo revisions, and it is hoped that it will be approved for publication in 1989.

The council sponsored a small invitational meeting, "Psychiatry and Managed Care: A Resource Symposium," in November 1988. Approximately 50 knowledgeable individuals provided their perspectives on various aspects of managed care, i.e., economics, service delivery, consumer needs, management, and government activities. It is hoped that the material offered can be synthesized into an informational product for APA members and district branches, and it is anticipated that recommendations made at the conference will be referred to appropriate APA components for further study. The symposium was developed by several representatives of the council, Board, and Assembly, and the steering committee was chaired by Dr. Naomi Goldstein.

The council will be forwarding to the joint Reference Committee a statement on psychiatrists' signatures. Many psychiatrists, especially those in organized settings, need the association to establish a standard which both protects them and enables them to provide interdisciplinary leadership. The entire health field is struggling with how to provide care to indigent persons. Psychiatry has much work to do to address the needs of the large population of chronically ill persons and homeless mentally ill persons. The council will prepare a strategy with which APA can lead society in providing psychiatric care for the poor. At the other end of the spectrum, the council has also been called on to consider how to fund long-term psychotherapy. This issue is legitimate, as some illnesses need such therapy. It is gratifying to be part of this knowledgeable and conscientious group of professionals on the council and components and to be part of the larger organization that encourages our work.

The Council on Psychiatry and Law

Howard Zonana, M.D., Chairperson

The council has been busy this year coming to closure on and initiating new projects relating to laws regulating psychiatric practices and to the use of psychiatric expertise in the resolution of legal issues.

The Subcommittee to Review the Insanity Defense submitted a final report to the council, which the council accepted with minor revisions. The Assembly had raised eight areas of questions about the original position statement, and the summary of the subcommittee's recommendation for each question follows.

1. *Disposition of acquittees who are not expected to benefit from psychiatric intervention.* Recommendation: Acquittees who are unable to be discharged to outpatient status should remain under psychiatric care in a hospital environment.

2. *Standards and guidelines for mandatory outpatient treatment for acquittees.* Recommendation: A supervised program of conditional release should be established in each jurisdiction. Special training, support, and other incentives should be offered to agencies willing to provide outpatient care of acquittees at the local level.

3. *Further study of the experience in the "Oregon system" for assessing acquittees for release and further care.* Recommendation: There are several systems for the safe management of acquittees as outpatients. For example, both Oregon and Maryland have well-functioning programs. Each state should develop a program with adequate checks, balances, and safeguards.

4. *Consideration of restoring the "volitional prong" of the standard for insanity, including an attempt to assess the available data on its effect on acquittal and on the prevention of abuse of the mentally ill.* Recommendation: Although there are concerns that the elimination of the "volitional prong" may have caused additional suffering to some severely mentally ill offenders, the subcommittee was unable to find any convincing evidence to warrant the reinclusion of the "volitional prong."

5. *Study of the issue of involuntary intoxication.* Recommendation: A special task force should be appointed to review this issue, which is fundamentally interwoven with the criminal justice system.

6. *Elaboration of the kinds of testimony and questions most appropriately addressed by "psychiatric experts."* Recommendation: The psychiatric expert witness should be allowed to explain the relationship between the person's mental disorder and behavior and to explain the evaluation and diagnostic process even if that explanation includes language which embraces the legal standard if it is defined as the "ultimate question."

7. *Renaming the verdict "not criminally responsible" instead of "not guilty by reason of insanity."* Recommendation: The subcommittee supports the use of "not criminally responsible because of mental disorder" or a similar term which indicates that the act was committed but the actor was not legally responsible because of mental illness.

8. *System exploration and recommendations regarding the development of a peer review mechanism for forensic psychiatry and of ethical principles and rational guidelines for psychiatric consultation and participation in trials and other legal processes.* Recommendation: The establishment of a peer review system for forensic psychiatry does not seem practical at this time. Use of the forensic ethical guidelines of the American Academy of Psychiatry and the Law would further assist the district branch and APA ethics committees.

The report covers each area in detail and includes a final recommendation. The council was concerned about the elimination of the "volitional prong" without a clear scientific basis for its removal. On the other hand, the council was equally concerned about reinserting it without any data on whether patients have in fact been harmed or whether the inaccuracies in the use of this prong have resulted in more acquittals that could be deemed inappropriate. The council noted that several studies were underway to evaluate statutory

changes in legal standards and burdens of proof. Because it is difficult to evaluate the effect of a change in the standard on the basis of the current data, it was felt that a formal change in the position statement should not be made until additional data were collected.

As to the recommendation that expert psychiatric witnesses be allowed to explain the relationship between the mental disorder and the legal standard, even if that includes the ultimate question, the council believes that experts should be allowed to give grounds for their conclusions when testifying and that this should remain the prime objective. At the present time the federal courts and a few states have adopted the rule that ultimate issue testimony in insanity defenses will not be permitted. It is not yet clear enough whether this has substantially hampered experts' ability to give meaningful testimony.

For these reasons, the council felt that these recommended changes should not at the present time result in a rewriting of the original insanity defense position paper but that ongoing review should continue. If it seems warranted, a new position paper could be formulated. This report was referred to the Assembly for its review.

As was reported to the APA membership in the *Journal* a year ago, the council's proposed model regulation concerning the patient's right to refuse treatment is still being reviewed by a representative group from the Assembly. The council reviewed a series of state court decisions that are beginning to establish a trend toward mandating judicial review of treatment refusal when such cases have reached appellate review. Given this trend, the council felt it was important that states which do not yet have mandated judicial review have some viable alternatives to recommend to state legislatures. For that reason the council, which initially proposed that these guidelines be formally adopted as APA policy, now requested the guidelines be approved as a resource document so it can be circulated in a timely fashion. This was approved by the joint Reference Committee in October.

The council is examining the issue of reporting mentally ill persons to departments of motor vehicles. As a first step, the council has reviewed various state laws regarding this issue and will contact other related medical specialty societies that have similar concerns. This discussion was precipitated by a review of several cases, such as *Naidu v Laird* (1), *Cain v Rijken* (2), and *Schuster v Altenberg* (3), in which a mental health professional was held liable when a patient or former patient was released from the hospital and later was involved in an automobile accident that resulted in the death of a third party.

The council has continued to review position statements generated by the Ad Hoc Committee on AIDS. The council felt that two interim position papers approved by the Board of Trustees warranted modification. The council will ask the new Commission on AIDS to review these modifications.

The *Committee on Confidentiality*, Aron Wolf, M.D., chairperson, has continued to act as watchdog on confidentiality concerns brought to its attention by various APA members. Additionally, the committee was asked by the council to develop guidelines regarding confidentiality in the context of third party evaluations. This issue arose during discussion by the council and review of *Satterwhite v Texas* (4), a Supreme Court case decision of the 1987-1988 session. In that case, a defendant was ordered to undergo an examination by a psychiatrist to determine his competency to stand trial, sanity at the time of the offense, and future dangerousness, all at the same time and before he consulted with his counsel. These same issues were also raised in *Powell v the State of Texas* (5). In that case the court noted, "The use of psychiatric or psychological examination to determine a defendant's competency to stand trial is a separate matter as far as the Fifth Amendment privilege is concerned and is

distinct from the use of a psychiatric or psychological examination to determine the defendant's culpability of responsibility for the crimes charged against him." The Committee on Confidentiality was asked to develop guidelines for this type of evaluation and for evaluations resulting from requests by civil courts or other agencies. When completed, these guidelines will become part of the *Guidelines on Confidentiality* approved by the Board of Trustees last year. The committee will also conduct a component workshop on this topic at the 1989 annual meeting.

Committee members, in conjunction with staff of APA's Office of Public Affairs, added four more vignettes regarding common problems with confidentiality and release of information to its videotape, which brings the total number of vignettes to seven. A copy of this enhanced videotape has been provided to each Area for educational uses at the district branch level. The videotape is also shown at the committee's booth in the Membership Resource Center at the annual meeting.

Two new task forces were created under the council this year. The *Task Force on Disclosure of Psychiatric Treatment Records in Child Custody Disputes*, Carl Malmquist, M.D., chairperson, has begun to examine the issue of access to a parent's psychiatric records in a child custody dispute. It is believed that if the psychiatrist-patient privilege is automatically waived by a parent seeking custody of a child insofar as that parent has placed his or her mental and emotional condition in issue, this could have a chilling effect on the parent's inclination to obtain psychiatric help. The case law to date is far from uniform in the jurisdictions that have analyzed the question. In brief, state precedent falls into two basic categories. One group of state courts maintains that a parent who contests custody can be said to have placed his or her own psychological condition as a parent in issue, thus invoking the general patient-litigant exception to the privilege. The other group of state courts holds that while the parent seeking custody does not automatically place his mental state in

issue, certain compelling circumstances, to be decided on a case-by-case basis, may require the privilege to yield for the best interest of the child. This task force, drawing on the expertise of both forensic and child psychiatrists, will produce a statement on the appropriate role of parents' psychiatric records in child custody disputes.

The *Task Force on Use and Misuse of Psychiatric Diagnoses in the Courts*, Seymour Halleck, M.D., chairperson, will address the general concern in our profession that psychiatric diagnoses are used in legal proceedings to reach conclusions that may not be justified by current scientific knowledge. It is often assumed that diagnostic categories, in themselves, tell the legal system a great deal about issues such as competency and responsibility when they may not. There is a need to clarify how various psychiatric diagnoses are or might be associated with various legal capacities. The assessment of such capacities, as distinct from diagnostic determinations, has not been spelled out in the previous diagnostic manuals. It is hoped the material derived from the task force can be incorporated into a section in *DSM-IV* and that such clarification will provide guidelines for more accurate and scientific use of psychiatric diagnoses in the courts.

The council is also beginning to review ethical principles regarding psychiatric testimony and consultative situations in which there is no patient-physician relationship. The American Academy of Psychiatry and the Law is planning to submit its ethical guidelines to APA for incorporation into APA ethical guidelines. The council will review these guidelines in conjunction with the Ethics Committee.

REFERENCES

1. Naidu v Laird, 539 A 2d 1064 (Del 1988)
2. Cain v Rijken 717 P 2d 140 (Ore 1986)
3. Schuster v Altenberg 424 NW 2d 159 (Wis 1988)
4. Satterwhite v Texas 56 LW 4470 (1988)
5. Powell v the State of Texas 742 SW 2d 353 (Tex 1987)

The Council on Research

John E. Adams, M.D., Chairperson

The Council on Research continues to hone its role as the arm of the Association most concerned with science policy, scientific assessment, and research issues. To reflect on these roles and on its own future, the council held a summer retreat (in addition to its regular semiannual meetings) to discuss a broad range of issues. Considerable time was spent focusing on the content and recommendations contained in the research chapters of the proceedings of the conference "The Future of Psychiatry," which was held in late 1987. The majority of these recommendations centered on issues of science policy—broadening the base of scientific knowledge and ensuring the future infrastructure of psychiatric research, including personnel, facilities, and instrumentation. Others emphasized the need to synthesize research findings in communications and education in a manner that conveys both the excitement and promise of ongoing research.

In keeping with its efforts to maintain liaison with the federal research agencies, the council met with key leaders of the agencies of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), including the administrator of ADAMHA and the directors of the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse. These meetings have identified issues

of mutual concern. The topics of discussion included advocacy efforts (particularly the recent success of increasing ADAMHA research appropriations), animal rights, research training, medical and lay educational needs, and the importance of the science mission and its self-regulation.

The council met with members of the Council on Medical Education and Career Development and the Committee on Graduate Education to discuss recruitment of residents into research careers and research experiences during residency training, respectively. Two main issues have been raised repeatedly with respect to the interaction of research training with general residency education. The first concerns identifying steps that can be taken to ensure residents are exposed to research, the research experience, and the issues in research which might encourage them to seek research careers during general residency. The second issue concerns the need to develop a flexible program that meets the requirements of the Residency Review Committee for Psychiatry and the American Board of Psychiatry and Neurology but allows residents with a serious interest in research to maintain and sharpen their research skills. The council, in conjunction with the Office of Research, plans to make a presentation at the upcoming meeting of the American Association of Directors of Psychiatric Residency Training to discuss

research training issues generally and to learn more about their concerns and activities.

The council, in conjunction with the Office of Research, hosted its second annual by-invitation-only breakfast for more than 125 young researchers at APA's 1988 annual meeting in Montreal. The breakfast, cosponsored by the Ittleson Foundation, focused on writing research grant proposals and also afforded informal interaction with senior research psychiatrists. After this breakfast, the kickoff session for the New Research portion of the program focused on science policy issues facing American and Canadian research agencies. The council met with representatives of the Scientific Program Committee at the fall component meetings to discuss plans for the 1989 annual meeting in San Francisco. The initial plans entail spotlighting the research of young investigators.

The council approved guidelines to ensure appropriate internal review of all research proposals developed by APA so that the political implications and possible conflicts of interest are examined before a study is undertaken.

The activities of all components under the aegis of the Council on Research follow. The Committee on Science Policy remained inoperative in the past year but should be fully functioning in 1989.

The *Task Force on Prevention Research*, Robert Rose, M.D., chairperson, began to examine this emerging field, summarize existing information, and identify prevention research opportunities. The final report of this component should be ready for publication in July 1989.

The *Committee on Psychiatric Diagnosis and Assessment*, Layton McCurdy, M.D., chairperson, undertook an intense review in the past year of whether or not the Association should begin work on DSM-IV. Pros and cons were carefully considered, and the committee ultimately recommended the establishment of a task force to begin work on DSM-IV (subsequently approved by the Board of Trustees in December 1987). The committee's own role in the DSM-IV process will be to oversee the work of the Task Force on DSM-IV. It will work at times as an appellate body to handle controversial issues and decisions and will also facilitate communication with internal and external groups about diagnostic issues generally. In addition to these DSM activities, the committee is also charged with appraising diagnostic and assessment approaches and generally with oversight of the other research component related to diagnostic assessment, the Task Force on the Use of Laboratory Tests in Psychiatry.

The committee formed a subgroup to consider and investigate cases in which the text or criteria of DSM-III-R have led to legal, administrative, or economic difficulties. It is exploring abuses of diagnostic categories with the Council on Psychiatry and Law, the Council on Children, Adolescents, and Their Families, the Council on National Affairs, and other relevant components.

The *Task Force on DSM-IV* was approved by the Board of Trustees in December 1987, and Dr. Allen Frances was appointed as chairperson in March 1988. The task force held its first meeting in May 1988. The task force consists of the chairperson, the chairperson of the individual work groups devoted to major diagnostic categories, and several additional at-large members. Each work group consists of approximately five individuals who have primary responsibility for a specific section of work. Consultants and advisors will be invited to assist the work groups and may include members of the minority caucuses, international experts, and members of other interested professional organizations. The chairpersons of the specific work groups are Drs. Nancy Andreasen (schizophrenia), John Rush (affective disorders), John Gunderson (personality disorders), Marc Schuckit (substance use disorders), Gary Tucker (organic disorders), Dennis Cantwell and Magda Campbell (childhood disorders), Robert Hales (somatoform, factitious, dissociative, and impulse control disorders), and Janet Williams (multiaxial diagnosis). The at-large members are Drs. Robert Spitzer, Roger Peele, Darrel Regier, and Kenneth Kendler. Dr. Spitzer also serves as a special advisor to the task force. Additional, more limited work groups may be appointed to tackle specialized areas of study, e.g., eating disorders, sleep disorders, late luteal phase dysphoric disorder.

The task force has already begun extensive communications and has written to all APA components and a number of outside organizations regarding DSM-IV issues. It has initiated ongoing commu-

nication with a wide network of groups and individuals and is planning presentations at the APA annual meeting and the H&CP Institute.

The task force and members of the World Health Organization (WHO) have been discussing the 10th edition of the *International Classification of Diseases* and its compatibility with DSM. Members of the task force and WHO representatives met in October at a conference sponsored by ADAMHA to discuss issues of mutual interest.

The *Task Force on the Use of Laboratory Tests in Psychiatry*, Alexander Glassman, M.D., has produced two reports since its inception: "The Dexamethasone Suppression Test: An Overview of Its Current Status in Psychiatry" (1) and "Tricyclic Antidepressants—Blood Level Measurements and Clinical Outcome: An APA Task Force Report" (2). The council has recommended that this component be disbanded with special thanks for its important accomplishments, and it is anticipated that the Board of Trustees will approve this request.

The *Committee on the Biographical Directory and Related Professional Activities Research (Manpower)*, Robert Dorwart, M.D., chairperson, has focused its attention in the past couple of years principally on the production of the next *Biographical Directory*. The committee received over 25,000 responses to the professional activities survey, which is a roughly 75% response rate. Data collection was closed the week of the 1988 fall component meetings, and the committee has begun to develop detailed plans for analysis of the data. It is anticipated that the *Directory* will be published in January 1989.

The *Committee on Research on Psychiatric Treatments*, John Kane, M.D., chairperson, is overseeing a number of treatment-related task forces that now report to it rather than directly to the Council on Research. These include the Task Force on Benzodiazepine Dependency, Task Force on Tardive Dyskinesia, Task Force on Electroconvulsive Therapy, Task Force on Psychosocial Treatment Research, and Task Force to Study the Long-Term Effects of Lithium on the Kidney. Summaries of the activities of these task forces are included in this report.

The committee sent each component a request for suggestions of treatment areas in the greatest need of assessment. It received a number of recommendations, but additional information is needed on many of them before further assessment needs can be determined. These areas include phototherapy, psychostimulants, the efficacy of psychotherapy, treatment of personality disorders, and maintenance treatment guidelines. The committee formed a small subgroup to review anticonvulsants in psychiatry and to prepare an article on this issue for publication.

Other matters the committee is considering include the lack of support for investigational therapies research, particularly for inpatient care, establishing linkage with the Food and Drug Administration (FDA), updating the psychopharmacological screening criteria in conjunction with the Committee on Quality Assurance, and research issues associated with APA's malpractice insurance.

The *Task Force on Benzodiazepine Dependency*, Carl Salzman, M.D., chairperson, has nearly completed its report. The task force will meet in December 1988 at the annual meeting of the American College of Neuropsychopharmacology to review the final draft, which will then be submitted to the Committee on Research on Psychiatric Treatments and the Council on Research for their review in early 1989. The task force plans to recommend that a condensed form of the report be submitted to the *American Journal of Psychiatry* and that the full report be published as an APA monograph. The task force has focused on the hazards of benzodiazepines, e.g., dependency, toxicity, discontinuance symptoms, and abuse. The task force submitted a proposal for a component workshop at the 1989 annual meeting so that it could share its findings and recommendations with the membership. The task force members agreed that there is a need to review the indications for and efficacy of benzodiazepines and that consideration should be given to either broadening the charge of the current task force or convening a new group. A recommendation to this effect may be made after the current report is completed.

The *Task Force on Tardive Dyskinesia*, John Kane, M.D., chairperson, has completed about 75% of its report. It covers epidemiology, risk factors, use of neuroleptics in special populations (e.g.,

geriatric patients), treatment, and alternatives to neuroleptic treatment. The chapters needing additional work concern the long-term course of tardive dyskinesia and research issues. The task force is still trying to develop videos for psychiatrists and for nonpsychiatric physicians, although requests for outside funding have not been as successful as desired. The task force expects that its report will be completed by the end of 1988.

The *Task Force on Electroconvulsive Therapy (ECT)*, Richard Weiner, M.D., chairperson, has been developing comprehensive clinical guidelines on ECT that will help the practitioner. Dr. Weiner anticipates that the guidelines will be circulated to the Committee on Research on Psychiatric Treatments, the Council on Research, the Assembly, and a number of outside experts and other relevant organizations for review in the fall of 1988. Comments from these groups will be considered, and the final document will be submitted to the Board of Trustees for approval in the spring of 1989 and to NIMH in the summer.

The task force continues its work with the FDA on the reclassification of ECT devices and met with representatives of the Center for Devices and Radiological Health in the spring to further this effort. The task force hopes that this long-standing issue will be resolved soon.

The *Task Force on Treatments of Psychiatric Disorders*, T. Byram Karasu, M.D., chairperson, has completed its report, which was approved by the Board of Trustees in September 1987. This work is being edited and should be ready for publication at the time of the 1989 annual meeting.

The *Task Force to Study the Long-Term Effects of Lithium on the Kidney*, George Heninger, M.D., chairperson, has had difficulty completing its report. The Committee on Research on Psychiatric

Treatments is working with this component to find solutions to the continual difficulties it has encountered.

The *Task Force on Psychosocial Treatment Research*, John Docherty, M.D., chairperson, continues to work on its report.

The *Task Force on Sudden Death*, George Simpson, M.D., chairperson, published its report, "Sudden Death in Psychiatric Patients: The Role of Neuroleptic Drugs," in the spring of 1988. Single copies of the report are available from the Office of Research at no cost. The task force was disbanded in June 1988 with appreciation for its accomplishments.

APA has received an increasing number of inquiries about the utility of quantitative electrophysiological techniques and the training required to interpret electrophysiologic measures. In response to a request by the Committee on Psychiatric Diagnosis and Assessment, the Council on Research agreed that it would be a good time to establish a task force on quantitative electrophysiological assessment and has recommended this to the Board of Trustees. If approved, this task force would report to the Council on Research through the Committee on Psychiatric Diagnosis and Assessment.

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1. The APA Task Force on Laboratory Tests in Psychiatry: The dexamethasone suppression test: an overview of its current status in psychiatry. *Am J Psychiatry* 1987; 144:1253-1262
2. Task Force on the Use of Laboratory Tests in Psychiatry: Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; 142: 155-162

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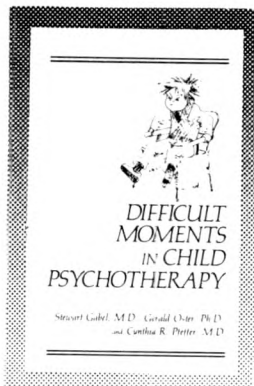
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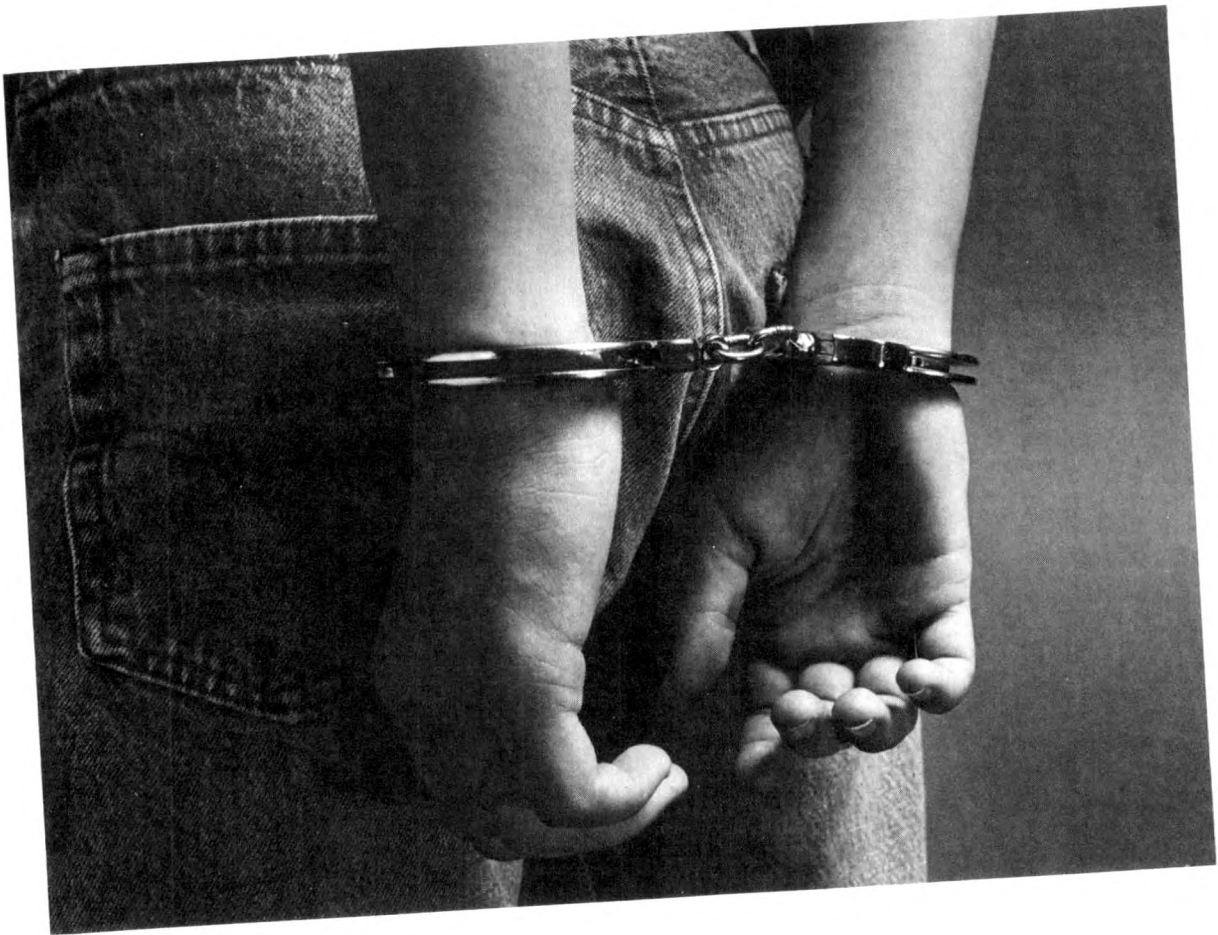
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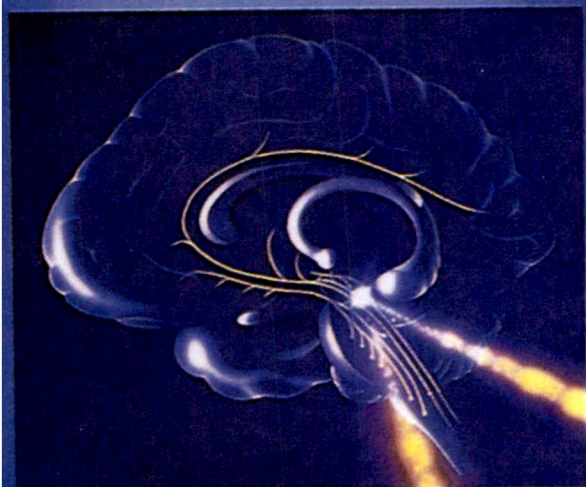
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1. *Curr Ther Res* 1986; 39:559-563.
*As defined by DSM-III.

*See adjacent page
for brief summary of
prescribing information.*

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Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors*—Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, cardiac tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknown at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General—Anxiety and Insomnia*—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac: Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected. Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—See Warnings.

Other Antidepressants—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and Slow Elimination under Clinical Pharmacology).

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (see Accumulation and Slow Elimination under Clinical Pharmacology).

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay, cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been established.

Usage in the Elderly—Prozac has not been systematically evaluated in older patients, however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hypotension—Several cases of hypotension (some with serum sodium lower than 110 mmol/L) have been reported. The hypotension appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: Commonly Observed—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=799)		Prozac (N=1,730)	Placebo (N=799)
Nervous			Body as a Whole		
Headache	20.3	15.5	Asthenia	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.8	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.2	1.1			
Sedated	1.9	1.3	Respiratory		
Sensation			Upper		
Disturbance	1.7	2.0	respiratory		
Libido			infection	7.6	6.0
Decreased	1.6	—	Flu-like		
Light-			syndrome	2.8	1.9
headedness	1.6	—	Pharyngitis	2.7	1.3
Concentration,			Nasal		
decreased	1.5	—	congestion	2.6	2.3
			Headache,		
Digestive			sinus	2.3	1.8
Nausea	21.1	10.1	Sinusitis	2.1	2.0
Diarrhea	12.3	7.0	Cough	1.6	1.6
Mouth			Dyspnea	1.4	—
Dryness	9.5	6.0			
Anorexia	8.7	1.5	Cardiovascular		
Dyspepsia	6.4	4.3	Hot flashes	1.8	1.0
Constipation	4.5	3.3	Palpitations	1.3	1.4
Pain,					
abdominal	3.4	2.9	Musculoskeletal		
Vomiting	2.4	1.3	Pain, back	2.0	2.4
Taste change	1.8	1.1	Pain, joint	1.2	1.1
Fatulence	1.6	1.1	Pain, muscle	1.2	1.0
Gastroenteritis	1.0	1.4			
			Urogenital		
Skin and			Menstruation,		
Appendages			painful	1.9	1.4
Sweating,			Sexual		
excessive	8.4	3.8	dysfunction	1.9	—
Rash	2.7	1.8	Frequent		
Pruritus	2.4	1.4	micturition	1.6	—
			Urinary tract		
			infection	1.2	—
			Special Senses		
			Visual		
			disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
— incidence less than 1%.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—Frequent: chills; Infrequent: chills and fever, cyst, face edema, hanger effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—Frequent: increased appetite; Infrequent: aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlohydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocytopenia.

Metabolic and Nutritional—Frequent: weight loss; Infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hypoproteinemia, and iron deficiency anemia.

Musculoskeletal System—Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—Frequent: abnormal dreams and agitation; Infrequent: abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buttioglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hyperreflexia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumscribed paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertension, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—Frequent: bronchitis, rhinitis, and yawn; Infrequent: asthma, epistaxis, hiccup, hyperpnea, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/atelectasis, and pleural effusion.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, laryngeal edema, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdose: Human Experience—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

PV 2472 DPP (111788)

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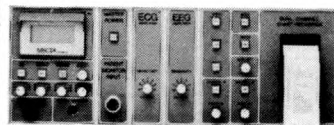
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London, England

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During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

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HALDOL DECANOATE (HALOPERIDOL) INJECTION

Sustained protection
for the schizophrenic patient
with a single monthly dose

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurotoxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence, at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: *Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions* have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy* is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia—As with all antipsychotic agents* HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia—Tardive dystonia*, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states* which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS). *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

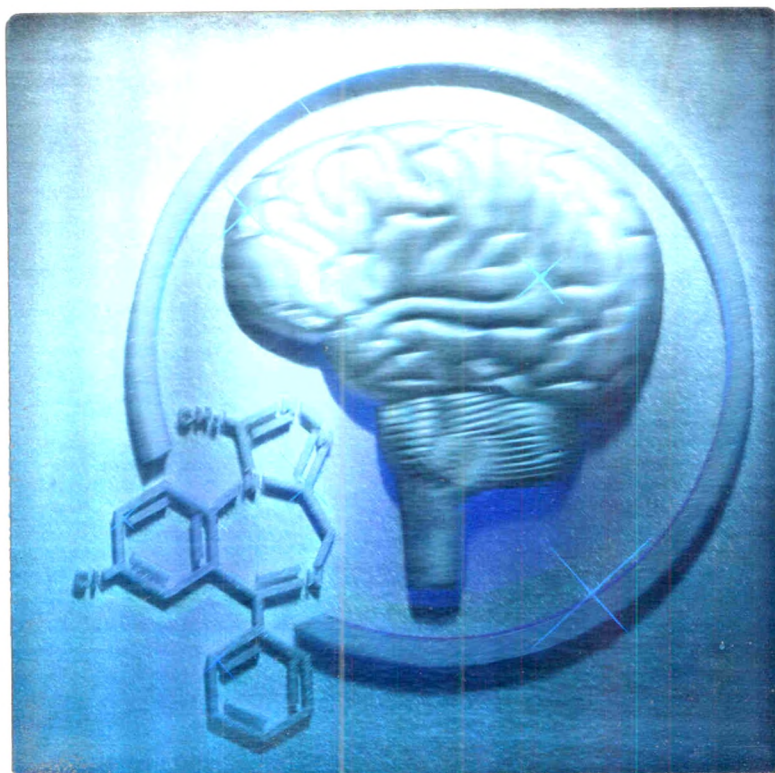
The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women; hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation; thus reduce dose gradually (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants consider drug potentiation (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients use the lowest possible dose (See Dosage and Administration). Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs; (b) possible fetal abnormalities; (c) operating machinery or driving; (d) not increasing dose of the drug due to risk of dependence; (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tired-

ness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea, vomiting and increased salivation. **Cardiovascular:** Tachycardia/palpitation and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation (See Warnings).

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrua irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship

was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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When Psychotic Features Complicate Depression, Simplify the Treatment With ASENDIN

A single agent for depression with psychotic features

"Amoxapine...is a weak blocker of dopamine receptors *in vivo* and *in vitro*. Such a drug might be especially useful in the treatment of psychotic depressions."¹ Elliott Richelson, MD *Journal of Clinical Psychiatry*, 1982

On the Brief Psychiatric Rating Scale, treatment with ASENDIN improved the condition of 86% of depressed patients with psychotic features.²

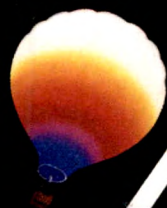
Single-blind study by Raymond F. Anton, MD, et al *Journal of Clinical Psychiatry Monograph*, 1986

A simple, easy-to-follow dosage schedule for depression with psychotic features

Suggested dosage in depression with psychotic features 100 mg bid. Adjust according to the clinical response and tolerance.*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information, on adjacent page, especially **Warnings** and **Information for the Patient** sections.



ASENDIN[®]

amoxapine

BRIEF SUMMARY
ASENDIN® amoxapine Tablets
25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hypertensive crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously with gradual increase in dosage until optimum response is achieved.

WARNINGS: **Tardive dyskinesia:** Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (i.e., antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substitutive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on **Information for the patient** and **ADVERSE REACTIONS**.)

Neuroleptic malignant syndrome (NMS): A potentially fatal symptom complex. NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (e.g., pneumonia, systemic infection) and inadequately treated extrapyramidal symptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotic and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of complications. If any of these signs or symptoms are present, the patient should be carefully monitored since recurrences of NMS have been reported. Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure.

Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia; changes in conduction time and rhythm; myocardial infarction and stroke have been reported with drugs of this class. Use extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Monic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. **Information for the patient:** It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness, performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. **Drug interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. **Therapeutic interactions:** Concurrent administration with electroshock may increase hazards associated with such therapy. **Carcinogenesis, impairment of fertility:** In a 21-month toxicity study at three dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. In rats, adenocarcinoma was detected in low incidence in the mid dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.

Pregnancy, Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. **Pediatric use:** Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies. Incidence greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%). Less frequently reported reactions were: **CNS and neuromuscular**—anxiety, insomnia, restlessness, nervousness, palpitations, tremor, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. **Allergic**—edema, skin rash. **Endocrine**—elevation of prolactin levels. **Gastrointestinal**—nausea. **Other**—dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence less than 1%—**Anticholinergic**—disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. **Cardiovascular**—hypotension, hypertension, syncope, tachycardia. **Allergic**—drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. **CNS and neuromuscular**—tremor, paresthesias of the extremities, tremor, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See **WARNINGS**.) **Hematologic**—leukopenia, agranulocytosis. **Gastrointestinal**—epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. **Endocrine**—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. **Other**—lacrimation, weight gain or loss, altered liver function, painful ejaculation. **Drug relationship unknown:** Reported rarely, but under circumstances where drug relationship was unknown. **Anticholinergic**—paralytic ileus. **Cardiovascular**—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. **CNS and neuromuscular**—hallucinations. **Hematologic**—thrombocytopenia, eosinophilia, purpura, peltichia. **Gastrointestinal**—paralytic ileus. **Endocrine**—change in blood glucose levels. **Other**—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

Additional adverse reactions reported with other antidepressant drugs: **Anticholinergic**—sublingual adenitis, dilation of the urinary tract. **CNS and neuromuscular**—delusions. **Gastrointestinal**—stomatitis, black tongue. **Endocrine**—gynecomastia.

OVERDOSEAGE: Signs and symptoms

Toxic manifestations of ASENDIN amoxapine overdose differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment Treatment of ASENDIN overdose should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al [N Engl J Med 1982; 306:1337-1340]. Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdose, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdose patients.

References 1. Richelson E. Pharmacology of antidepressants in use in the United States. J Clin Psychiatry. 1982; 43:4-11.

2. Anton RF, Hitt A, Diamond B, et al. Amoxapine treatment of psychotic depression: dose effect and dopamine blockade. J Clin Psychiatry Monograph 1986; 4:32-36.

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1. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. *Arch Gen Psychiatry* 1977; 34:314-320
2. McNamara JR (ed): *Behavioral Approaches to Medicine*. New York, Plenum Press, 1979
3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

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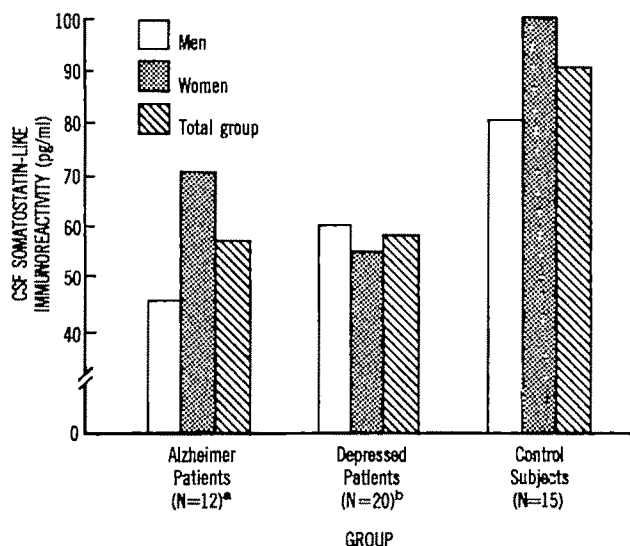
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FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



^aSignificant difference between men and women ($t=1.31$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

^bSignificant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

duced to 40.5 picas (6¾ inches). When space on the horizontal axis is insufficient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
3. Error bars should not be used.
4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.
5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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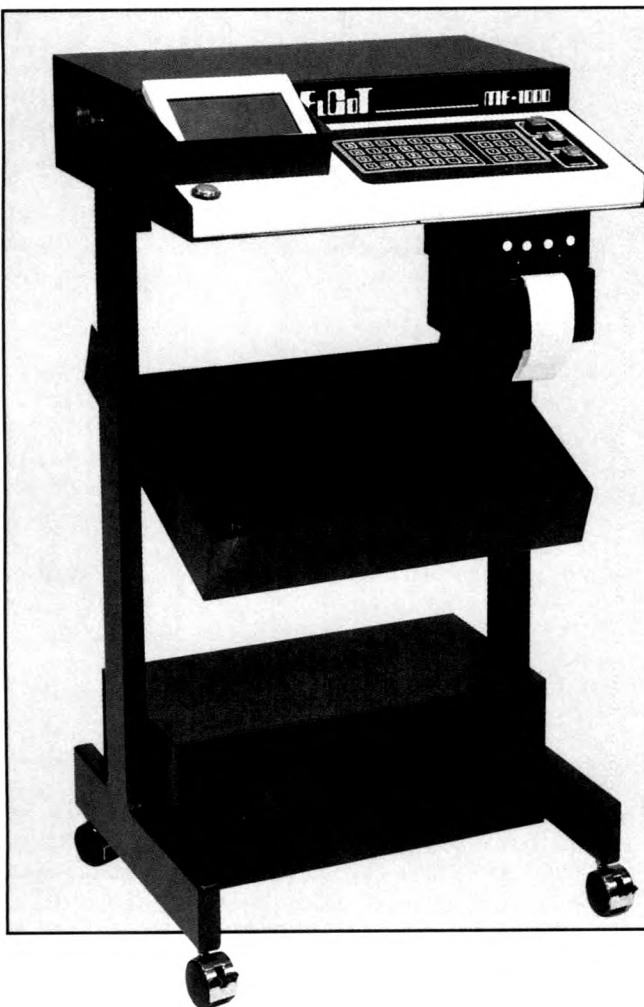
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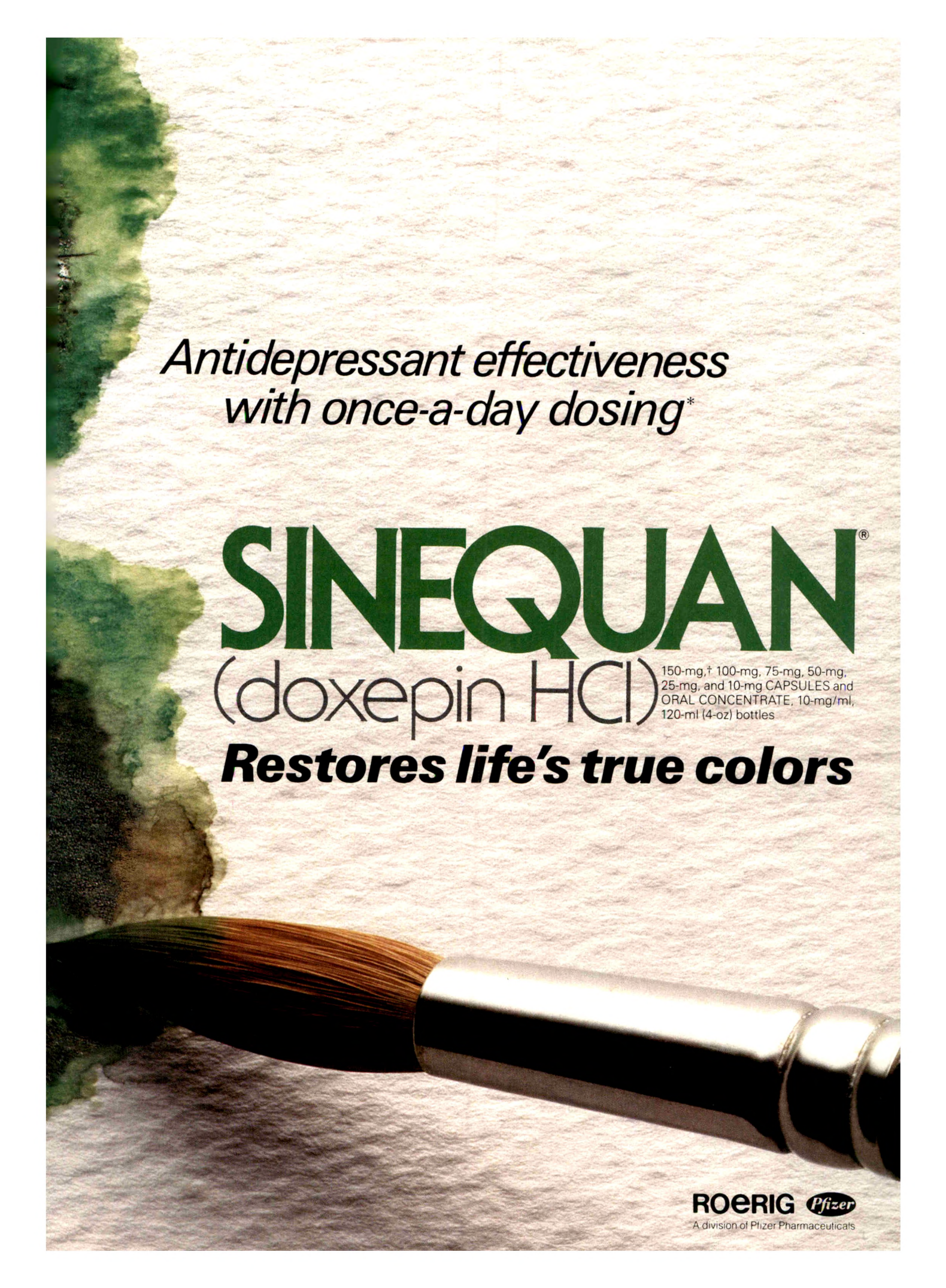


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms. The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdose consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdose due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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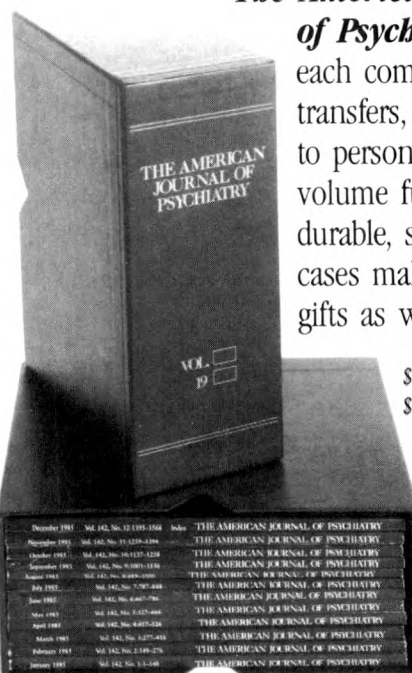
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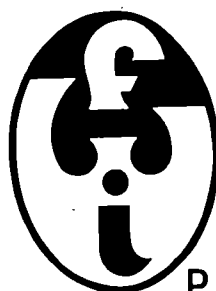
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Book Reviews



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*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias, bone marrow depression, liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) Intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium meglumine. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonia, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dyskinesia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecoma, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

SK&F CO.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 4 April 1989

In this issue:

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By Herbert Pardes, Charles A. Kaufmann, Harold Alan Pincus, et al.

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By Glen O. Gabbard

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By Lawrence W. Smith and Joel E. Dimsdale

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Contraindications: Hypersensitivity to buspiron hydrochloride.

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Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspiron will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspiron withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspiron's binding to dopamine receptors: Because buspiron can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the

syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspiron; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspiron; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspiron does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspiron was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspiron did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspiron is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation in-

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The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

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cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: Tachycardia/palpitations 1%. *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal*: Musculoskeletal aches/pains 1%. *Neurological*: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin*: Skin rash 1%. *Miscellaneous*: Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of

breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

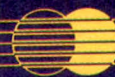
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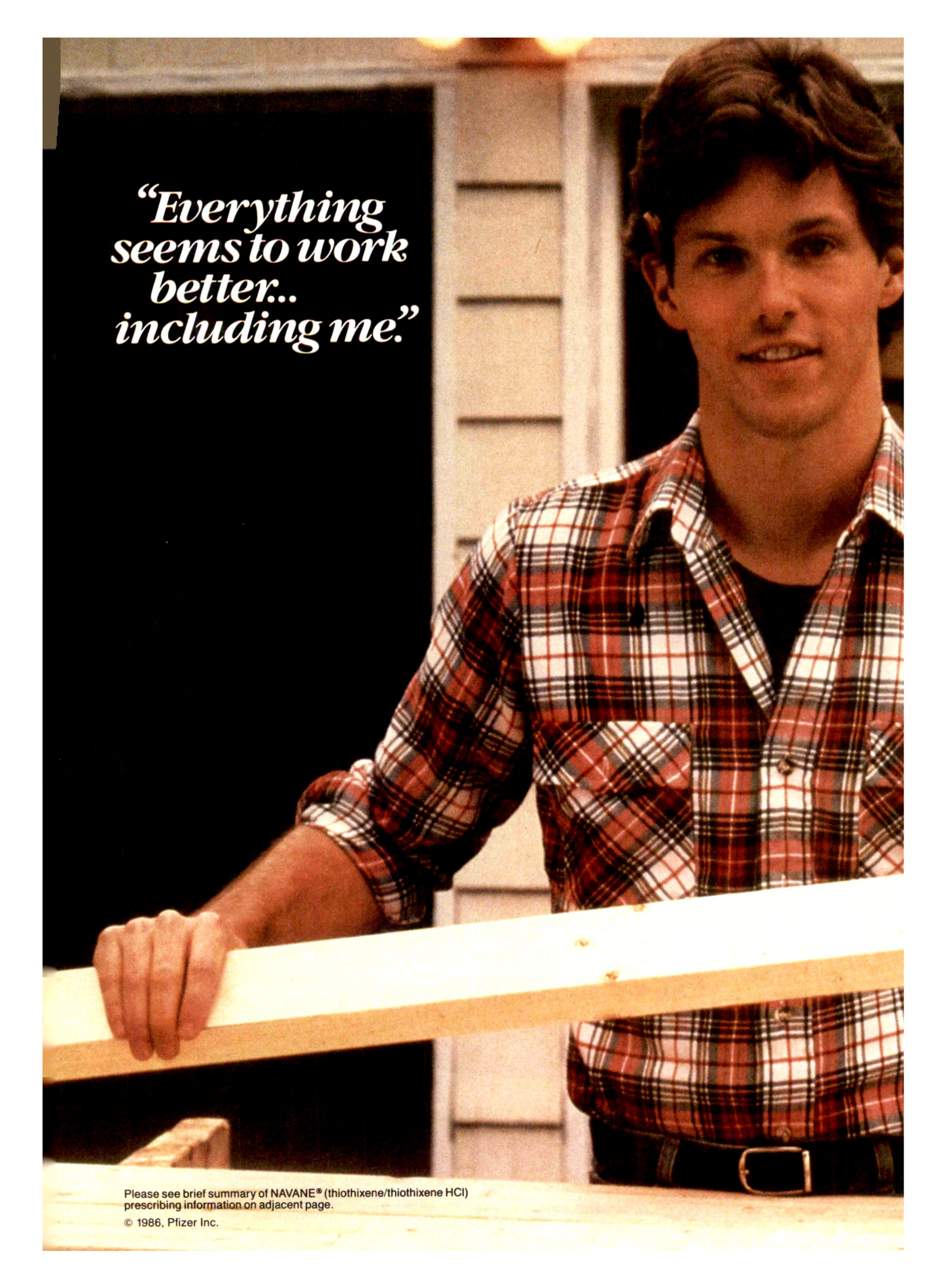
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A color photograph of a young man with dark, wavy hair, wearing a red, white, and black plaid button-down shirt over a dark t-shirt. He is leaning his right arm on a light-colored wooden railing. The background is slightly out of focus, showing what appears to be a doorway or a window with white trim. The lighting is warm and indoor.

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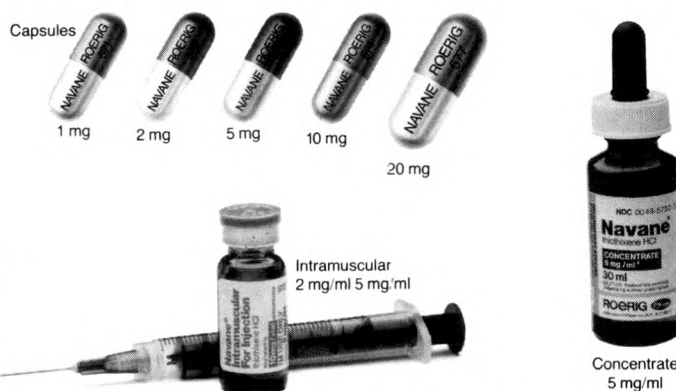
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Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Use in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Use in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Non-specific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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New York, New York 10017

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Rapid tranquilization with a wider margin of safety.

Although neuroleptic agents provide an effective means of controlling violent or destructive behavior, their use is associated with a risk of serious and potentially irreversible adverse effects.¹⁻² Dose reduction is the best way to minimize this risk, but such a solution may not be possible during an emergency. The use of ATIVAN Injection combined with a low-dose neuroleptic provides an alternative pharmacologic approach for sedating anxious and agitated patients exhibiting severely disruptive behavior.

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Ativan® Injection: Pharmacologically desirable as an adjunct for sedation.

Unlike other benzodiazepines, ATIVAN Injection is readily absorbed following intramuscular administration,⁴ with peak plasma concentrations occurring in approximately 60 to 90 minutes.⁵ Mean half-life is about 16 hours and the desired sedative and anxiolytic effects usually last 6 to 8 hours.^{5*}

*The additive central-nervous system effects of neuroleptics should be borne in mind when used concomitantly with ATIVAN Injection.

Please see the adjacent page for a brief summary of prescribing information.

Ativan® Injection I.M.

(lorazepam) C_{IV}

**Calm the patient,
curtail adverse reactions.**

ATIVAN® INJECTION I.M. (LORAZEPAM) ©

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative. **CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2 to 4 mg lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling preoperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15 to 20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6 to 8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of morphine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances when the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse (See WARNINGS and ADVERSE REACTIONS).

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8 to 10 mg of IV lorazepam (2 to 2.5 times maximum recommended dose) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with penicillins 150 and 75 mg. Although this study showed both lorazepam and penicillins interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce anesthesias resulting in gangrene which may require amputation (See WARNINGS).

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IN LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION, THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide) is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hypotension and laryngeal reflexes.

PREGNANCY: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlorazepate, diazepam, meperidine) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for pre-anesthetic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g., phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection (See CLINICAL PHARMACOLOGY and WARNINGS). Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION). When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose (See ADVERSE REACTIONS).

Information for Patients: As appropriate, inform patients of pharmacologic effects, e.g., sedation, relief of anxiety and lack of recall, and duration of these effects (about 6 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and may interfere with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials, no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, electrolytes, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total protein.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g., narcotic analgesics, inhalation anesthetics, scopolamine, atropine and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility. **Pregnancy:** Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidences varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasions (3/1580), patient was unable to give personal identification on arrival in operating room, and one patient left when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (later seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (145/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular Systems: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory Systems: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary under-ventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over a prolonged period of time may result in limited physical and psychological dependence.

OVERDOSEAGE: Overdose of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypoxia, stages one to three coma and, very rarely, death. Treatment of overdose is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSEAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedication, usual IM doses of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS). For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for preoperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other injectable CNS depressants should ordinarily be reduced (See PRECAUTIONS). For optimum effect, measured as lack of recall, IV lorazepam should be administered 15 to 20 minutes before anticipated operative procedure.

EQUIPMENT NECESSARY TO MAINTAIN A PATIENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) Injection, Wyeth, is available in single- and multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 1 ml and 10 ml vials and 1 ml fill in 2 ml TUBEX.

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Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Ejecture entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogeneous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

CI 3261-2 6/22/83

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For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

JUNE

June 1, The Institute for Addiction Studies presents "Adult Children of Alcoholics: Theory & Practice," Oakland, California. Contact Stephanie Ross, MPI CDRH, 435 Hawthorne Avenue, Oakland, CA 94609; 415-428-4104.

June 1-3, 8th Society for Menstrual Cycle Research Conference, Salt Lake City. Contact Ann Voda, University of Utah, 25 South Medical Drive, Salt Lake City, UT 84112; 801-581-8272.

June 9-11, Part II Examinations, American Board of Psychiatry and Neurology, Denver. Contact Stephen C. Scheiber, M.D., Executive Secretary, 500 Lake Cook Road, Suite 335, Deerfield, Illinois 60015.

June 11-14, 15th Congress of the International Association for Suicide Prevention, Brussels. Contact European Congress Consultants and Organizers, Rue Vilain XIII, 17A, Brussels B-1050, Belgium.

June 12-13, "Mental Health Services for Children and Adolescents in Primary Care Settings: A Research Conference," Hartford, Connecticut. Contact Phil Leaf, Ph.D., Yale Psychiatric Institute, 350 Congress Avenue, New Haven, CT 06519; 203-785-5551.

June 14-16, 12th Annual Convention of the International Psychohistorical Association, New York. Contact Professor Samuel S. Janus, Ph.D., Chair, Program Committee, P.O. 2247, Charlottesville, VA 22902; 804-971-8086.

June 14-16, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Minneapolis. Contact Dianne Weitzel, Department of Psychiatry, University of Minnesota, UMHC Box 393, 420 Delaware Street, S.E., Minneapolis, MN 55455; 612-626-6015.

June 15-18, annual meeting, American Association of Neuropathologists, Dallas. Contact Reid R. Heffner, Jr., M.D., Executive Director, 462 Grider Street, Buffalo, NY 14215; 716-898-3117.

June 18-21, 16th Annual Conference, National Council for International Health, "Toward a Healthier World: Influencing International Policies and Strategies," Arlington, Virginia. Contact Conference Department, National Council for International Health, 1701 K Street, N.W., Suite 600, Washington, DC 20006.

June 18-22, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn Street, Chicago, IL 60610; 312-645-5000.

June 19-21, annual meeting, Committee on Problems of Drug Dependence, Inc., Keystone, Colorado. Contact Martin W. Adler, Ph.D., Executive Secretary, 3420 North Broad Street, Philadelphia, PA 19140; 215-221-3298.

June 19-22, 1st World Conference in Family Therapy: "Divisions, Conflicts, Resolutions," Dublin. Contact Helen Haughton, Conference Chairperson, 5 Clare Street, Dublin 2, Ireland; or Florence W. Kaslow, Ph.D., President, International Family Therapy Association, 2617 North Flagler Drive, Suite 204, West Palm Beach, Florida 33407.

June 19-23, 14th International Congress of Gerontology, Acapulco, Mexico. Contact Viajes S.G., S.A. de C.V., Avenue Cuauhtemoc 1135 Col. Del Valle, Mexico City, 03650, Mexico; 604-78-15.

June 21-24, International Symposium on Alzheimer's Disease, Wurzburg, West Germany. Contact Department of Psychiatry, Fuchsteinstr. 14, D-8700 Wurzburg, Federal Republic of Germany.

June 21-24, 7th International Symposium on "Adapted Physical Activity—An Interdisciplinary Approach," Berlin. Contact 7th ISAPA Berlin '89, Institut fur Sportwissenschaft, Rheinbabenalle 14, D-1000 Berlin 33, West Germany; 030-824-3731.

June 24-27, annual meeting, American Nurses' Association, Kansas City, Missouri. Contact Judith A. Ryan, Ph.D., R.N., Executive Director, 2420 Pershing Road, Kansas City, MO 64108; 816-474-5720.

June 25-30, 15th International Congress on Law and Mental Health, Jerusalem. Contact Congress Organizers International, Ltd., P.O. Box 29313, 65121 Tel Aviv, Israel.

June 28-July 2, World Congress of Cognitive Therapy, Oxford, United Kingdom. Contact Dr. A.D. Kidman, Neurology Unit, University of Technology—Sidney, Westbourne Street, Gore Hill, N.S.W. 2065, Australia; 02-436-6238.

(Continued on page A22)



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References: 1. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* May 1977; 34:607-612. 2. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine*. August 1983; 51:87-109. 3. Georgotas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive textbook of psychiatry* IV. Baltimore, Md: Williams & Wilkins, 1985; 1821-833. 4. Blackwell B, Peterson GR, Kuzma RJ, Hosteller RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol*. 1980; 4:255-261. 5. Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol*. 1978; 6:155-161. 6. Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry*. 1982; 17:535-546. 7. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm*. 1986; 5:471-480. 8. Roose SP, Glassman AH, Siris SG, Walsh BT, Bruno RL, Wright LB. Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol*. 1981; 1:316-319. 9. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th ed. New York, NY: Macmillan Publishing Co. 1985; 413-423. 10. Thaysen P, Bjerre M, Kragh-Sorensen P, et al. Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology*. 1981; 74:360-364.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor[®] (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor[®] (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time, myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such

as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy: Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children: Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms, in overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment. In this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: Cardiovascular: Hypotension, hypertension,

tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, panic, nightmares, hypomania, exacerbation of psychosis. **Neurologic:** Numbness, tingling, paresthesias of extremities, incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms, seizures, alteration in EEG patterns, tinnitus. **Anticholinergic:** Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention, delayed micturition, dilation of the urinary tract. **Allergic:** Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. **Hematologic:** Bone marrow depression, including agranulocytosis; eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. **Endocrine:** Gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, testicular swelling, elevation or depression of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Jaundice (simulating obstructive), altered liver function, weight gain or loss, perspiration, flushing, urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue, headache, parotid swelling, alopecia. **Withdrawal Symptoms:** Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM 217-1/13/89]



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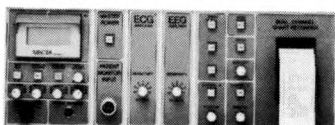
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Calendar

(Continued from page A16)

JULY

July 9–13, 10th Biennial Meeting of the International Society for the Study of Behavioral Development, Jyväskylä. Contact Department of Psychology, University of Jyväskylä, SF-4100 Jyväskylä, Finland.

July 16–21, 2nd International Conference on Health Law and Ethics, American Society of Law and Medicine, Commonwealth Lawyers' Association, and Commonwealth Medical Association, London. Contact American Society of Law and Medicine, 765 Commonwealth Avenue, Suite 1634, Boston, MA; 617-262-4990.

July 20, Institute for Addiction Studies presents "Chemical Dependency and Family Dynamics: COAs, ACAs, Myths and Issues," Oakland, California. Contact Stephanie Ross, MPI CDRH, 435 Hawthorne Avenue, Oakland, CA 94609; 415-428-4104.

July 28–29, Cook County Graduate School of Medicine presents "Psychotropic Medication—Do's and Don'ts in Everyday Clinical Practice," Chicago. Contact Francois E. Alouf, M.D.; in Illinois, 800-621-4649, outside Illinois, 800-621-4651.

AUGUST

August 7–12, International Congress on "Therapy with Amino Acids and Analogues," Vienna. Contact Prof. G. Lubec, MA 17, Allgemeines Krankenhaus, Währinger Gürtel 18-20, 1090 Wien, Austria.

August 21–25, World Congress on Mental Health, World Federation for Mental Health, Auckland, New Zealand. Contact Richard Hunger, World Federation for Mental Health, 1021 Prince Street, Alexandria, VA 22314-2971; or Dr. M. Abbott, Mental Health Foundation, P.O. Box 37-438 Parnell, Auckland, New Zealand.

August 27–September 2, 10th International Congress, International Association of Group Psychotherapy: "Encounter or Alienation," Amsterdam. Contact Jay W. Fidler, M.D., 362 Old York Road, Flemington, NJ 08822.

August 29–September 1, 1st Congress, World Union of Professions, Montreal. Contact Services de Congres GEMS, C.P. 1016, Succ. Snowdon, Montreal, P.Q., Canada H3X 3Y1; 514-485-0855.

When Psychotic Features Complicate Depression, Simplify the Treatment With ASENDIN

A single agent for depression with psychotic features

"Amoxapine...is a weak blocker of dopamine receptors *in vivo* and *in vitro*. Such a drug might be especially useful in the treatment of psychotic depressions."¹ Elliott Richelson, MD *Journal of Clinical Psychiatry*, 1982

On the Brief Psychiatric Rating Scale, treatment with ASENDIN improved the condition of 86% of depressed patients with psychotic features.²

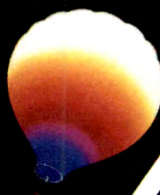
Single-blind study by Raymond F. Anton, MD, et al *Journal of Clinical Psychiatry Monograph*, 1986

A simple, easy-to-follow dosage schedule for depression with psychotic features

Suggested dosage in depression with psychotic features 100 mg bid. Adjust according to the clinical response and tolerance.*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information, on adjacent page, especially **Warnings** and **Information for the Patient** sections.



ASENDIN[®]
amoxapine

BRIEF SUMMARY
ASENDIN (amoxapine tablets)
 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is understood in animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Imipramine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolites, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hypertensive crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptics (i.e., antipsychotic drugs). Amoxapine is not an antipsychotic, but it has substantial neuroleptic activity. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, of the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If neuroleptic treatment is withdrawn, neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these concerns, neuroleptic treatment should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatment are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptic, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information on treatment of tardive dyskinesia and its clinical detection, please refer to the sections on Information for the Patient and ADVERSE REACTIONS.)

Neuroleptic malignant syndrome (NMS): A potentially fatal symptom complex, NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse rate, tachycardia, dysrhythmias, and cardiac dysrhythmias). Diagnosis is complicated. Rule out medical causes (e.g., pneumonia, systemic infection) and inadequately treated neuroleptic symptoms.

Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotics and other drugs not essential to maintain patient safety, intensive symptomatic treatment and medical monitoring, and treatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsychotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of NMS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intracranial pressure.

Watch patients with cardiovascular disease closely. Tricyclic antidepressants, particularly in high doses, can produce arrhythmias, changes in conduction time, and cardiac arrhythmias. In addition, there have been reports with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; antipsychotic patients may develop increased symptoms of psychosis. Patients with a history of convulsive disorders may have such symptoms exacerbated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause arrhythmias and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. Information for the patient: It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Women patients of potential childbearing age should be advised of the potential risk of such drugs on the fetus.

Operating machinery should be avoided. Drug interactions: See CONTRAINDICATIONS regarding concurrent use of tricyclic antidepressants and monoamine oxidase inhibitors. Anticholinergic effects may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. Therapeutic Interactions: Concurrent administration with electroshock may increase hazards associated with such therapy. Concomitantly, impairment of fertility: In a 21-month study of these dose levels in rats, pancreatic test cell hyperplasia occurred with slightly increased incidence of dose 5-10 times the human dose. The human dose was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in uterine cycle length.

Pregnancy, Proliferation: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetal effects (prelacteal death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between day 4-7) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no data on the use of ASENDIN in pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. Pediatric use: Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies: (side effects greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (14%), and blurred vision (7%).

Less frequently reported reactions were: CNS and neuromuscular—anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, dizziness, ataxia, ataxia in EEG patients. Allergic—urticaria, skin rash. Endocrine—elevation of prolactin levels. Gastrointestinal—nausea. Other—dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence less than 1%—Anticholinergic—disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. Cardiovascular—hypotension, hypertension, syncope, tachycardia. Allergic—drug fever, urticaria, photosensitization, purpura, rarely vasculitis, hepatitis. CNS and neuromuscular—tremor, weakness of the extremities, trismus, discoloration, seizures, hypomania, rumination, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See WARNINGS.) Hematologic—leukopenia, agranulocytosis. Gastrointestinal—epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. Endocrine—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other—lacrimation, weight gain or loss, altered liver function, painful ejaculation. Drug relationship unknown: Reported rarely, but under circumstances where drug relationship was unknown: Anticholinergic—paralytic ileus, Cataplexy—cataplexy—cataplexy (including ataxia), myocardial infarction, stroke, heart block, CNS and neuromuscular—hallucinations, Hysteria—hysteria, cyanosis, ecchymosis, purpura, petechiae, Gastrointestinal—paralytic ileus, Endocrine—change in blood glucose levels. Other—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, ataxia.

Additional adverse reactions reported with other antidepressant drugs: Anticholinergic—sublingual edema, dilation of the urinary tract. CNS and neuromuscular—delirium. Gastrointestinal—stomatitis, black tongue. Endocrine—gynecomastia. OVERDOSEAGE: Signs and symptoms:

Tolerant manifestations of ASENDIN overdose are different significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitute a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdose in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment: Treatment of ASENDIN overdose should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdose, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdose with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdose patients.

References: 1. Richelson E: Pharmacology of antidepressants in use in the United States. J Clin Psychiatry 1982;43:4-11. 2. Anton RE, Hill A, De Armentis A: The neuroleptic treatment of psychotic depression: dose effect and dopamine blockade. J Clin Psychiatry Monograph 1986;4:32-36.

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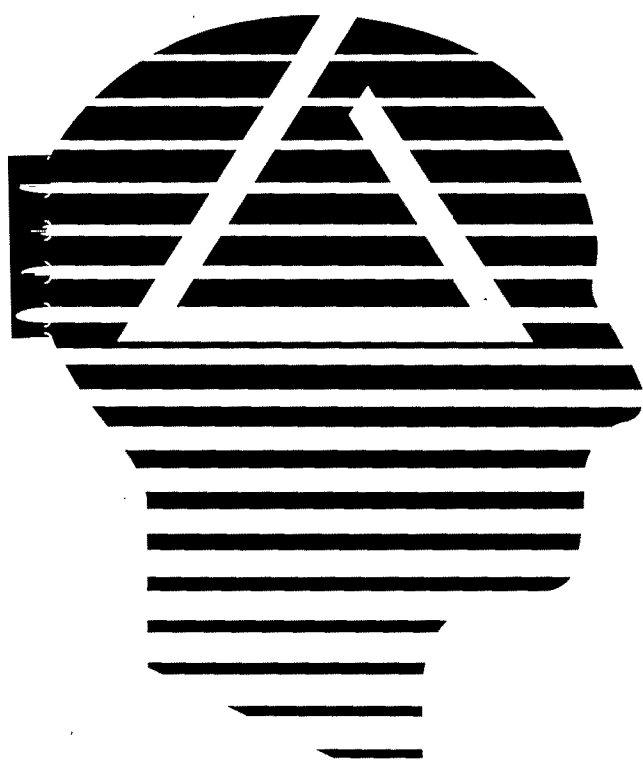
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As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

VALIUM® (diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is

VALIUM® (diazepam/Roche)

unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. **Adults:**

Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500.

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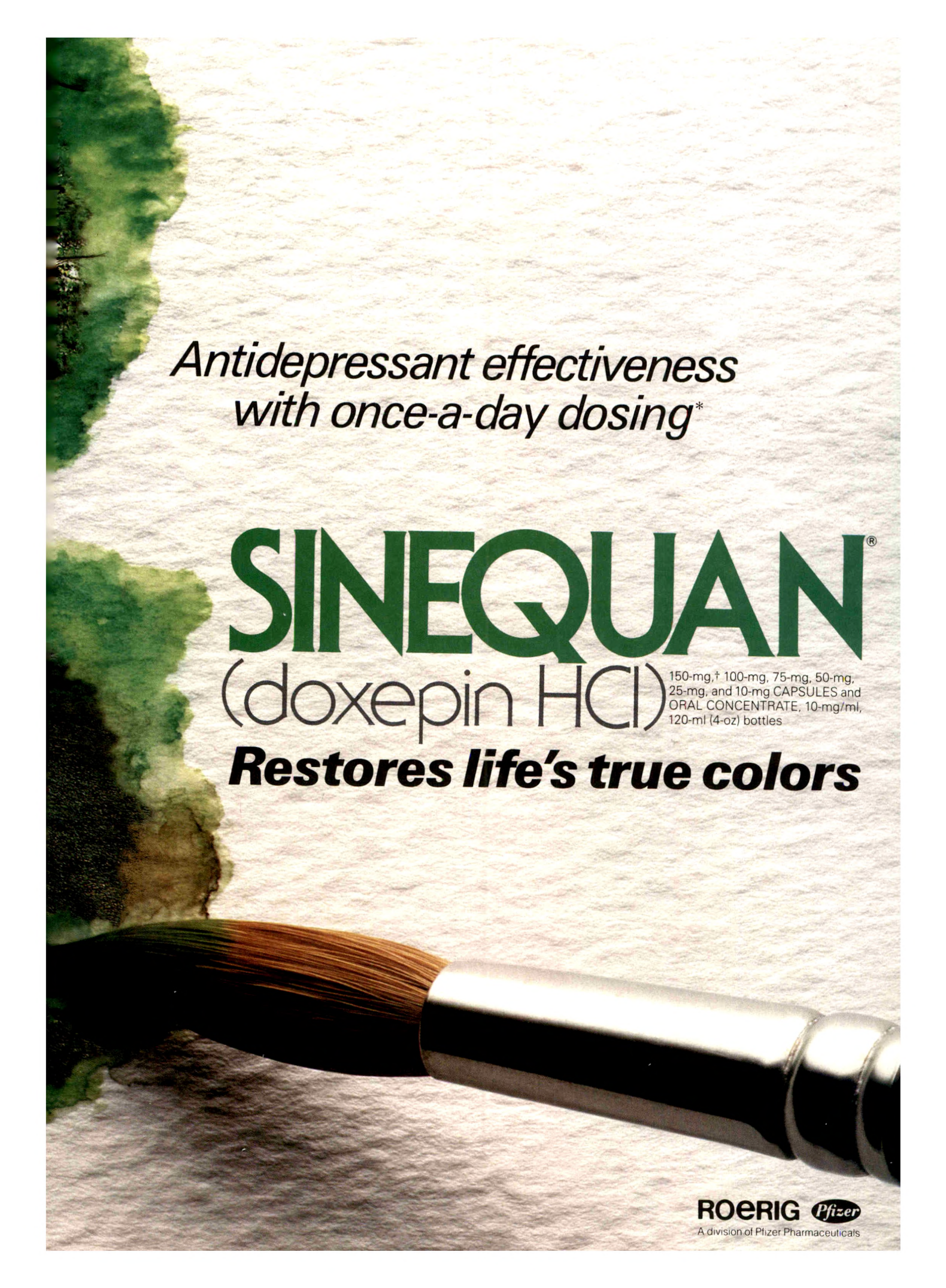


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intermittent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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American Psychiatric Association

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October 15-19, 1989

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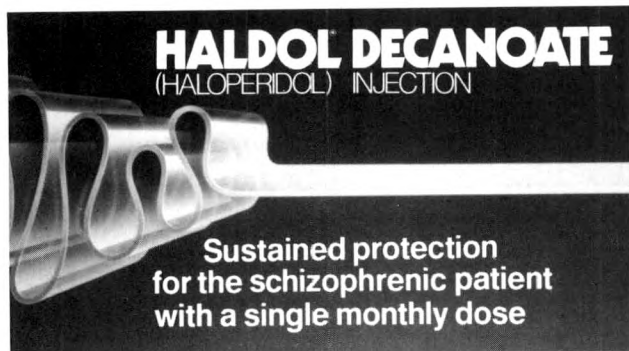
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**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

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McNEILAB, INC., Spring House, PA 19477



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL, as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracranial pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL. The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurotoxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

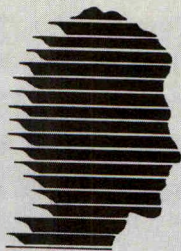
CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Extrapyramidal symptoms may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation** of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—As with all antipsychotic agents** HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—Tardive dystonia**, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states** which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdose, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.



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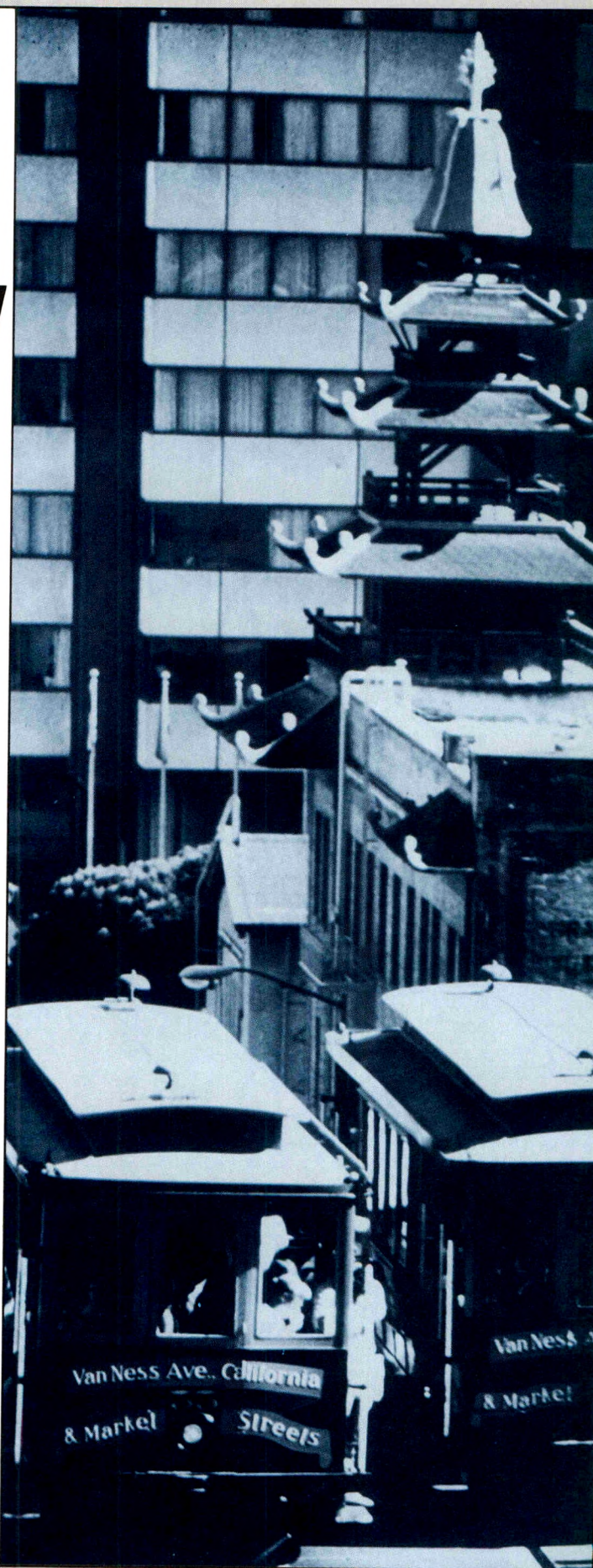
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As an organization accredited by the ACCME to sponsor continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 4 credit hours in Category 1 for the CME requirement of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.

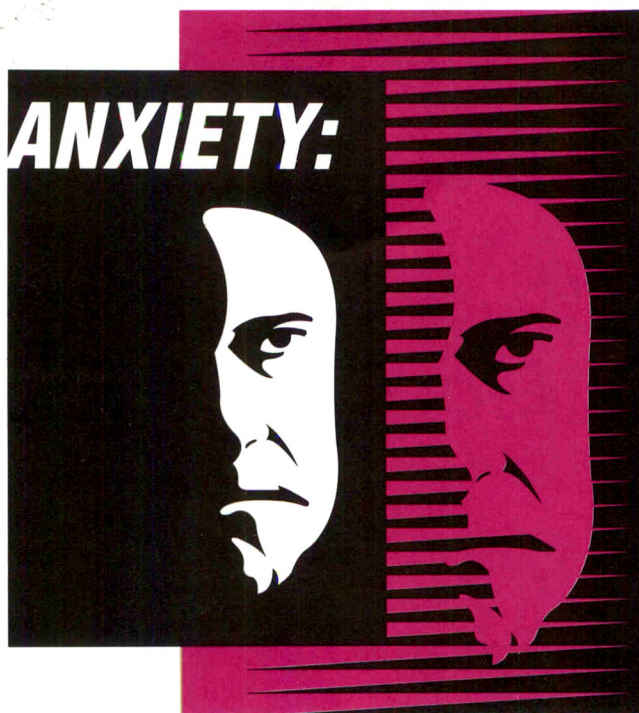
The American
Psychiatric Assoc.
Sunday, Monday
Tuesday, Wednesday
May 7-10, 1989
Grand Ballroom
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San Francisco, CA



Supported by an educational grant from **MeadJohnson** Pharmaceuticals

Chairperson

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Adult Psychiatry Clinical Services
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May 7-10, 1989

6:30 AM Breakfast
7:30-8:30 AM Symposium

Continental Ballroom
San Francisco Hilton
San Francisco, California

The Silent Partner

Sunday, May 7, 1989
Anxiety and AIDS

Opening Comments

Paul Jay Fink, MD
Chairman, Department of Psychiatry
Albert Einstein Medical Center
Philadelphia, Pennsylvania
Medical Director,
Philadelphia Psychiatric Center
President, American
Psychiatric Association

**Anxiety and Stigmatizing Aspects
of HIV Infection**

Mindy Fullilove, MD
Assistant Clinical Professor of
Psychiatry and Epidemiology
UCSF School of Medicine
San Francisco, California

**Anxiety and the Neuropsychiatry
of AIDS**

Francisco Fernandez, MD
Chief, Psychiatric
Consultation Service
St. Luke's Episcopal Hospital
Assistant Professor of Psychiatry
Baylor College of Medicine
Houston, Texas

Monday, May 8, 1989
Anxiety and The Family

Opening Comments

John A. Talbott, MD
Professor and Chairman
Department of Psychiatry
University of Maryland
School of Medicine
Baltimore, Maryland
Past President, American
Psychiatric Association

**Family Anxiety and Victims of
Traumatic Events**

Lenore Cagen Terr, MD
Clinical Professor of Psychiatry
UCSF-Langley Porter
Neuropsychiatric Institute
San Francisco, California

**Family Anxiety and Parental
Cancer**

Jimmie Holland, MD
Professor of Psychiatry
Cornell University Medical College
Chief, Psychiatry Service
Memorial Sloan Kettering
Cancer Center
New York, New York

Tuesday, May 9, 1989
Anxiety and Substance Abuse

Opening Comments

Daniel X. Freedman, MD
Judson Braun Professor of
Psychiatry and Pharmacology
Director, Division of
Adult Psychiatry
UCLA School of Medicine
Los Angeles, California
Past President, American
Psychiatric Association

Anxiety and Drug Abuse
**Professor Sir Martin Roth, MD,
ScD, FRC Psych**
Fellow of Trinity College
University of Cambridge
Cambridge, England

Anxiety and Alcoholism

V. Markku I. Linnoila, MD, PhD
Clinical Director
Division of Intramural Clinical and
Biological Research
National Institute on Alcohol Abuse
and Alcoholism
Alcohol, Drug Abuse and Mental
Health Administration
Bethesda, Maryland

Wednesday, May 10, 1989
Anxiety and Physical Illness

Opening Comments

Louis Jolyon West, MD
Professor and Chairman
Department of Psychiatry and
Biobehavioral Sciences
Director, Neuropsychiatric Institute
UCLA School of Medicine
Los Angeles, California

**Anxiety and Coronary Heart
Disease in Midlife**

Richard H. Rahe, MD
Professor of Psychiatry
Department of Psychiatry and
Behavioral Sciences
University of Nevada
School of Medicine
Reno, Nevada

**Anxiety and Physical Illness in the
Elderly**

James Turnbull, MD, FRCP (C)
Professor and Chairman
Department of Psychiatry and
Behavioral Sciences
Quillen-Dishner
College of Medicine
East Tennessee State University
Johnson City, Tennessee

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CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants consider drug potentiation (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose (See Dosage and Administration). Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs; (b) possible fetal abnormalities; (c) operating machinery or driving; (d) not increasing dose of the drug due to risk of dependence; (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tired-

ness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. **Cardiovascular:** Tachycardia/palpitations and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation (See Warnings).

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecostasia and galactorrhea have been reported but no causal relationship

was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy by no more than 0.5 mg every three days.

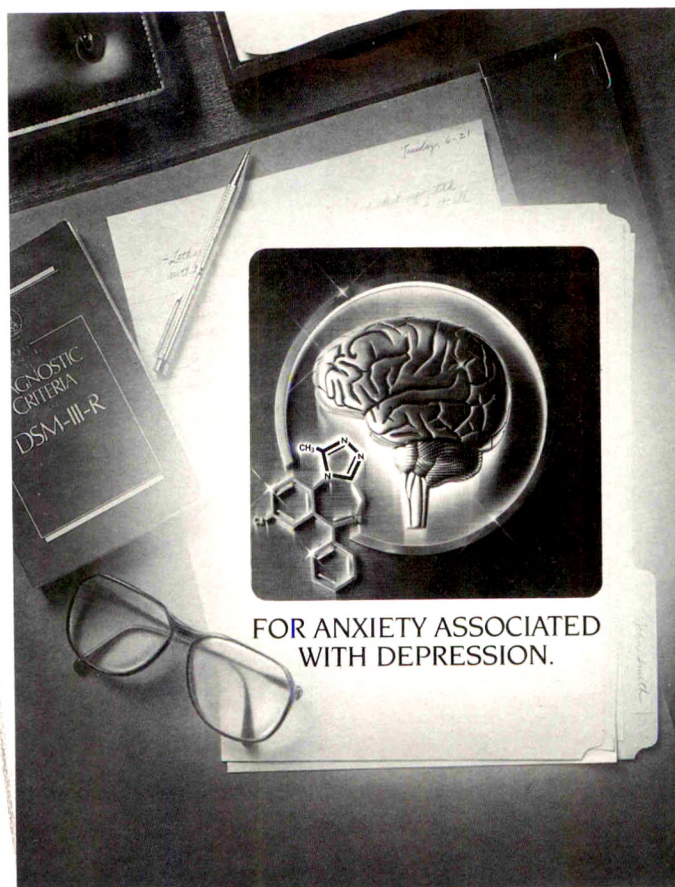
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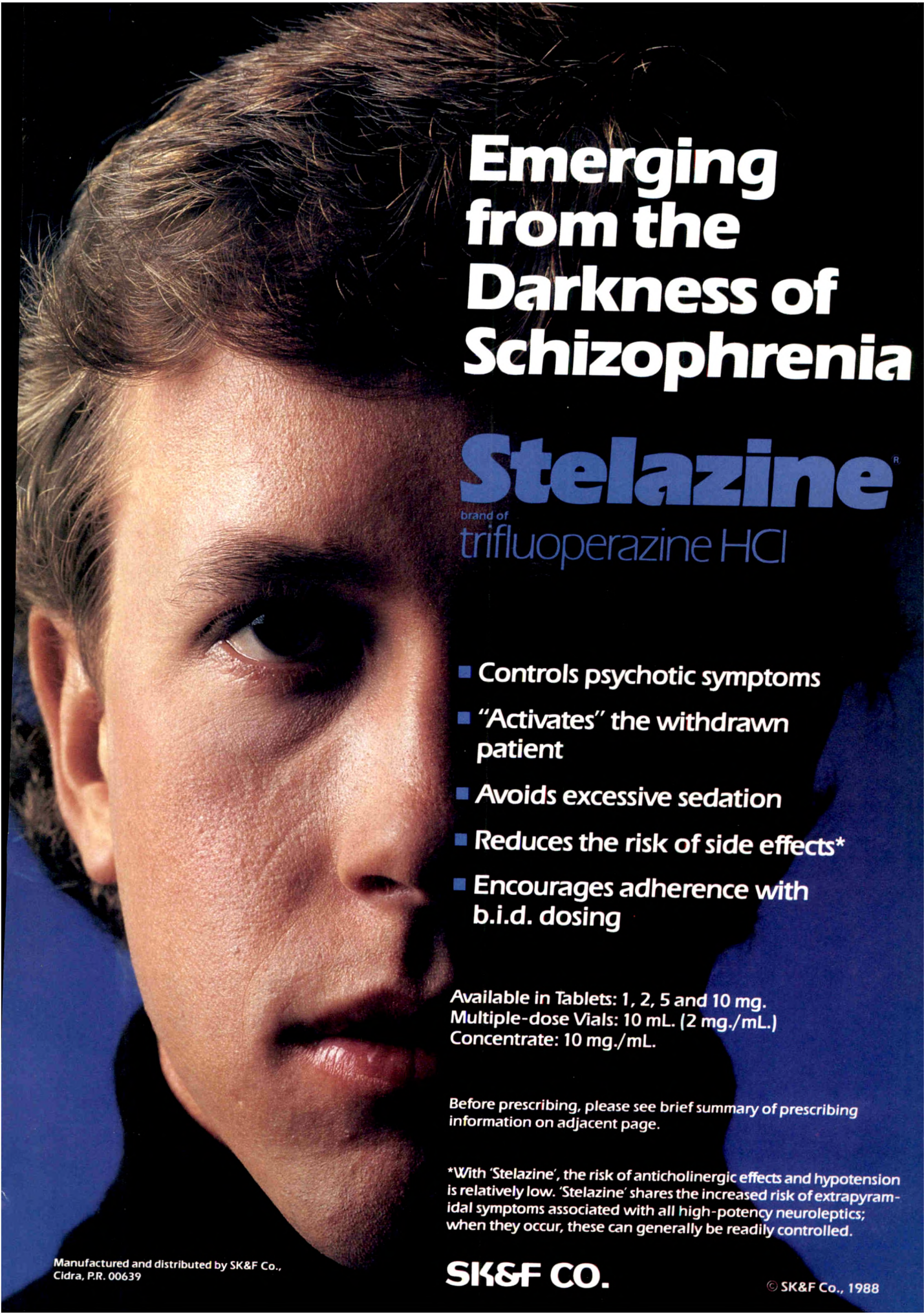
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Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuation of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, dynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecostasia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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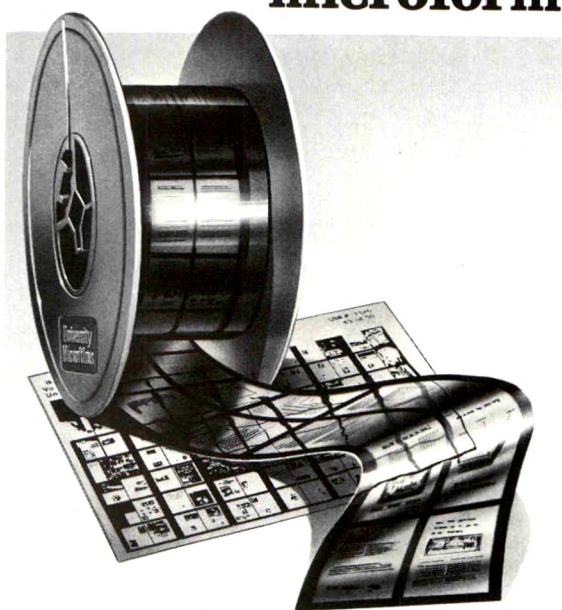
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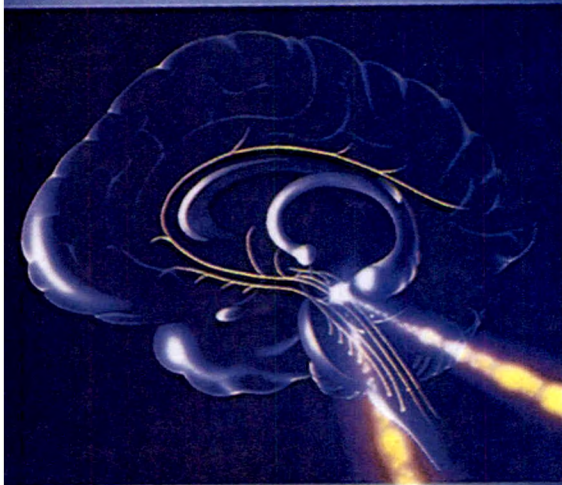
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1. *Curr Ther Res* 1986;39:559-563.
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Genetics and Psychiatry: Past Discoveries, Current Dilemmas, and Future Directions

Herbert Pardes, M.D., Charles A. Kaufmann, M.D.,
Harold Alan Pincus, M.D., and Anne West

Family, twin, and adoption studies have suggested an important role for hereditary factors in the etiology and pathogenesis of several psychiatric disorders. Advances in molecular and statistical genetics may very well reveal the identity of these factors, which may include single genes. Linked markers, critical to the discovery of abnormal genes in several medical conditions, have been reported for Huntington's disease, Alzheimer's disease, bipolar disorder, and schizophrenia. Psychiatric disorders pose particular problems (etiologic heterogeneity, incomplete penetrance, variable expressivity) for genetic research. New practical and ethical questions also arise. Nevertheless, knowledge may emerge that will suggest new approaches to diagnosis, prevention, and treatment.

(Am J Psychiatry 1989; 146:435-443)

Psychiatry is being transformed by genetic research. In particular, molecular genetic strategies are expected to reveal much about the etiology and pathogenesis of mental illness. We hope to learn in the foreseeable future both how the disposition to mental illness is transmitted and the biological basis of the inherited factors. This knowledge may make it possible

to intervene early with people at risk and to develop new approaches to prevention and treatment. Psychiatrists will likely be called upon to counsel individuals in whose families hereditary psychiatric disorders occur and to help them address the questions that evidence of risk status will pose.

Our purpose here is to describe, in brief, the evidence for a genetic component in several mental illnesses. Because molecular genetics has evolved so rapidly, we also briefly review this field and its contribution to psychiatry so far. We then highlight some current studies that are laying the groundwork for future, increasingly sophisticated genetic investigations. Finally, we consider some of the issues that may arise for psychiatric clinicians when people are faced with unprecedented and often painful genetic knowledge.

One problem created by the rapid advances in genetic research is how to assign priorities: which illnesses to study most vigorously, given limited resources. In this paper, we have chosen as examples chiefly, but not exclusively, the work being done on four major categories of psychiatric illness: schizophrenia, bipolar affective disorder, alcoholism, and panic disorder. Because there is strong evidence for genetic transmission of these disorders and because the disruption they cause is so great, we believe that these particular research efforts make an appropriate focus for this review.

APPROACHES TO PSYCHIATRIC EPIDEMIOLOGY

There are several stages in the research strategies necessary to clarify the role of genes in psychiatric disorders, and there are several methods of evaluating data. Each has certain strengths and certain limitations.

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Family Studies

Family studies can provide the first evidence that genes are involved in producing an illness. The morbid risk (adjusted prevalence) of the illness is determined within families, and the rate for patients' relatives is compared with that for relatives of control groups or for the general population. Reliable estimates of risk for patients, their families, and control groups have depended on the availability of operationalized diagnostic criteria, such as those in *DSM-III-R* and the Research Diagnostic Criteria.

First-degree relatives (parents, siblings, and offspring) of patients with bipolar affective disorder are reported to be at least 24 times more likely to develop bipolar affective illness than relatives of control subjects (1). Family studies of several other psychiatric disorders have shown that first-degree relatives of patients are at substantially higher risk: nine times higher risk for panic disorder (2), 10 times higher risk for alcoholism (3), and 18 times higher risk for schizophrenia (4).

In themselves, family studies cannot establish that an illness is hereditary. Familial aggregation may also reflect a shared environment, for example, common exposure to a virus or to a culture. However, family studies have suggested that several psychiatric disorders are *likely* to have a genetic basis.

Twin Studies

Twin studies compare the concordance rate for illness in pairs of monozygotic twins with the rate in dizygotic twins (and, in some studies, other first-degree relatives). The underlying assumptions of these analyses are 1) that monozygotic twins share all the same genes, while dizygotic twins, on average, have only half their genes in common, and 2) that both types of twins are exposed to the same (prenatal and postnatal) environment. One would expect monozygotic twins to show greater concordance for hereditary disorders than dizygotic twins.

Twin studies of schizophrenia have consistently reported at least a threefold greater risk for illness in monozygotic twins of patients than in dizygotic twins of patients and a 40- to 60-fold greater risk in monozygotic twins than in the general population (5). Controversy remains about the extent to which environmental factors can be considered equal for monozygotic and dizygotic twins. The in utero experience of monozygotic and dizygotic twins may differ (e.g., the former share placental circulation, whereas the latter do not). Moreover, monozygotic twins may not only share their genetic endowment but also elicit similar treatment from the environment by virtue of that endowment.

Nevertheless, the difference in concordance rates between monozygotic and dizygotic twins strongly supports the supposition of a genetic component in schizophrenia. Twin studies have reported concordance for

illness in 79% of monozygotic twins of patients with bipolar affective disorder, in contrast to 19% of dizygotic twins of such patients (6), in 26% of monozygotic twins of patients with alcoholism, in contrast to 12% of dizygotic twins (7; but see reference 8 for divergent findings), and in 31% of monozygotic twins of patients with panic disorder, in contrast to 0% of dizygotic twins (9).

Adoption Studies

Adoption studies and cross-fostering studies attempt to separate the contribution of nature and nurture by studying children raised away from their biological parents. Instances of adopted children developing the disorder of a biological parent and instances of biological relatives (but not adoptive relatives) developing the disorder of ill adoptees support the involvement of a genetic factor.

Adoption studies of alcoholism have shown substantially greater alcohol abuse by both male and female offspring of alcoholic biological parents than by offspring of control parents (10, 11). The biological relatives of schizophrenic adoptees have been reported to be at considerably higher risk for schizophrenia and related disorders than the biological relatives of matched control adoptees (12). Adoption studies of bipolar disorder and other affective illnesses showed a greater prevalence of psychiatric illness among biological but not adoptive relatives of adopted-away patients than among their respective control groups (13).

A limitation of adoption studies is that many of the most convincing data can only be obtained when the illness studied requires institutional care, thus providing investigators with hospital as well as adoption records. For pervasive but generally less incapacitating disorders, such as anxiety disorders, these data do not exist. Another problem with adoption studies is that environmental factors (including in utero environment) have already impinged on an adopted child. Further, there is likely to be a higher rate of psychiatric illness among all biological parents who give up children for adoption, including the "normal" control parents, than among adoptive parents, who usually undergo psychiatric screening by agencies.

Despite the limitations of any one of these studies, in aggregate they have yielded evidence for a genetic role in a number of mental illnesses. The problem now becomes to decipher how each illness is transmitted and what, biologically, constitutes the heritable factor.

MODE OF INHERITANCE

Possible Models

Genetic research throughout the medical disciplines has shown that more than 3,000 illnesses are monogenic (caused by defects in a single major gene) and are

transmitted according to Mendelian patterns (dominant, recessive, or sex-linked). A substantial number of these illnesses, approximately 25%, affect mental functioning (14). However, the appearance of any one of them (e.g., the Lesch-Nyhan syndrome or phenylketonuria) is fairly rare. In contrast, more common illnesses, such as atherosclerosis and diabetes, are believed to be inherited polygenically, that is, through the combined effects of several genes; there is reason to think that many psychiatric disorders fall into this category. Height and intelligence, for example, are both polygenically determined. The other likely mode of inheritance for widespread illness is multifactorial, that is, based on major and minor gene effects in combination and also on the interaction between heredity and environment.

Determining which of these models applies, and also how genetic and epigenetic factors may interact in mental illness, poses a number of problems, which we discuss later in this paper.

Methods of Analysis

A variety of statistical approaches, including segregation and linkage analysis, are being used to search both for the mode of inheritance and for the approximate chromosomal location of major genes predisposing to psychiatric disorder.

Segregation analysis (15) is one of the most powerful statistical methods in population genetics. The method compares the observed frequency of an illness in a pedigree with the pattern that would occur if a hypothesized mode of inheritance (e.g., one of the monogenic patterns or polygenic transmission) were true.

Despite its power and promise, segregation analysis has several limitations. It may be compromised by etiologic heterogeneity (see section on Future Directions in Psychiatric Genetics), which would invalidate pooled family data or population data. For this reason, it may be relatively insensitive to single-gene effects. So far, it has been unable to conclusively prove or refute monogenic inheritance for either schizophrenia (16) or major depression (17). Nevertheless, because searching for a single major gene defect may well be the most straightforward avenue of genetic research, this route continues to be explored by psychiatric geneticists.

Some investigators (18) argue that linkage analysis may be more sensitive than segregation analysis in detecting monogenic inheritance of mental illness. The search for disease-related genes may proceed, generally speaking, along three lines. Originally, genetic abnormalities were sought through the "protein/gene" approach. When an abnormal protein was found to accompany a given illness, this presumed abnormal gene product was used as a clue to the genetic lesion. Using this method, investigators found several separate defects in the gene that codes for the protein hypoxanthine phosphoribosyltransferase in different patients with the Lesch-Nyhan syndrome (19). Unfortunately, this approach has not yet fulfilled its potential in the

context of neuropsychiatric illnesses because, in all but a few instances, the metabolic concomitants of these illnesses are still unknown.

Conversely, the "gene/protein" approach begins by identifying the comparatively small area of the genome within which the disease gene lies. Radiolabeled probes—relatively short sections of DNA with known chromosomal locations—are used to seek out complementary nucleic acid sequences. If one of these is a sequence consistently transmitted with the disease (i.e., "linked" with the presumed aberrant gene), the approximate chromosomal location of the gene is revealed. After the approximate location of a disease gene has been established, a variety of techniques, summarized in the next section, permit increasingly precise localization of the gene.

The third research route is to study "candidate" genes: genes believed to be implicated in pathogenesis. Any abnormal biological feature, or "biological marker," associated with the disorder of interest may be postulated to arise from either an abnormal gene product or the product of a gene "linked" (by its proximity) to an actual disease gene (20). If the genomic region that codes for this linked feature is known, it permits a more direct search for an offending gene.

This approach has been fruitful in studies of familial Alzheimer's disease. It was found that β -amyloid protein accumulates in the brains of patients with Alzheimer's disease and of patients with Down's syndrome. Studies of chromosome 21, where the chromosomal abnormality responsible for Down's syndrome was known to be, led to localization of the gene for β -amyloid protein (21). This finding narrowed the search for a gene underlying familial Alzheimer's disease, which was found near, albeit not coincident with, the β -amyloid gene (22).

The biological marker approach is being brought to bear on several major mental illnesses. Hypercortisolemia has been associated with affective disorder in a number of studies (23). When the gene for the precursor peptide (pro-opiomelanocortin) of the pituitary hormone regulating cortisol secretion was cloned, it was quickly put to use in linkage studies of both bipolar illness and schizophrenia (24). Other candidate genes of potentially great importance in psychiatry include the genes encoding dopamine receptors (25), abnormalities of which have been implicated by many studies in the pathogenesis of schizophrenia (26), and those controlling receptor polypeptides of γ -aminobutyric acid, a major inhibitory neurotransmitter that may play a critical role in anxiety disorders.

The Genetic Endowment

There has been exponential growth in the number of molecular markers available for linkage studies. In fact, at the time of this writing, there are almost enough to make it possible to localize any major gene. These rapid advances have been made possible by the identification of restriction enzymes. These are bacte-

rial molecules that recognize and cut DNA at specific nucleic acid sequences, producing "restriction fragments" of characteristic lengths. Inherited DNA sequence variations (polymorphisms) among individuals cause these specific sequences to appear (or disappear), which in turn causes restriction fragments to vary. The variations can be detected by radiolabeled molecular probes, as we have described in connection with the gene/protein approach. The DNA sequences used as probes can be sequences either that code for proteins or that derive from noncoding regions of the genome (which constitute about 95% of genetic material). When the probe binds to a DNA fragment, the probe/fragment combination, known as a restriction fragment length polymorphism (RFLP), is considered a genetic marker.

Some 900 molecular probes have been assigned to autosomal gene locations, and some 130 probes have been identified on the X chromosome. For approximately 75% of these, not only has the chromosomal assignment been made, but the region of the chromosome where the probe's complementary sequence is located is also known.

When an RFLP cosegregates with illness in members of a family in which a hereditary disease occurs, it could represent a disease gene mutation or it could be a linked marker. Whether a marker is close enough to be considered linked to the gene is estimated by the frequency of genetic recombination, or crossover. Recombination is a process by which, during meiosis, sequences of DNA are exchanged between homologous chromosomes, thereby varying the characteristics inherited by the offspring. The smaller the distance between a gene and the RFLP of interest, the less likely it is that the two will be separated during this process. A "recombination fraction" is the percentage of cases in a pedigree in which crossover does occur. In these individuals, the marker and the characteristic believed to be caused by the gene are not inherited together. If the recombination fraction is large (e.g., 50%), the gene and the restriction site are not close enough to be considered linked. One form of linkage analysis applies the likelihood method, a statistical procedure that determines whether a recombination fraction of less than 50% could have occurred by chance (27).

After the general chromosomal location of a disease-associated gene has been established, researchers delimit the search further by means of chromosome "walking," chromosome "hopping" or "jumping" (28), and pulse-field electrophoresis. But even within a relatively narrow region on the chromosome, there may be more than 100 genes, any one of which might be the gene in question. There may also be a considerable amount of noncoding material. To narrow the region further—enough to identify a single abnormal gene—it becomes necessary to identify potentially relevant DNA sequences in the region.

There are several starting points for this process. 1) Often, coding regions begin at "CpG islands," non-methylated DNA sequences that can be identified by

their sensitivity to cleavage by certain restriction enzymes (29). 2) If a DNA sequence has been found in a number of phylogenetically diverse species, it is reasonable to presume that the sequence has fundamental biological importance. 3) If the messenger RNA derived from the gene has a disease-appropriate neuro-anatomical distribution (as shown by techniques such as *in situ* hybridization), it is reasonable to suspect it as a contributor to neuropsychiatric illness.

As more linked markers are identified in patients and their relatives, the prospect improves for locating the molecular lesion(s) responsible for pathogenesis. In the next few years, geneticists expect to "saturate" the human genome, that is, construct a map with known markers at regular intervals of approximately 10 centimorgans (cM) (1 cM corresponds to 1% recombination). The ultimate goal is to identify not only the gene but also the manner of its mutation in affected individuals.

There is reason to believe that gene defects in several neuropsychiatric illnesses, including Huntington's disease, Alzheimer's disease, and bipolar affective disorder, may be found soon, because closely linked RFLPs have been identified for the putative gene, or genes, in each.

PRACTICAL APPLICATIONS OF MOLECULAR GENETIC TECHNOLOGY

The genetic abnormality that causes Huntington's disease was localized in 1983 on chromosome 4 (30) by using molecular genetic methods to analyze an unusually large Venezuelan pedigree. Since then, a pre-symptomatic test for Huntington's disease, based on the presence of this RFLP, has become available. The same technology led to localization on chromosome 21 of a gene for familial Alzheimer's disease (22). In 1987 two teams of investigators reported two different genes responsible for producing manic-depressive illness, one among the Amish community in Pennsylvania and one in Israel. In the former (31), a gene inherited by autosomal dominant transmission was positioned on chromosome 11, near the gene for insulin. In the latter (32), the gene defect was localized on the X chromosome near the genes for color vision and the enzyme glucose-6-phosphate dehydrogenase.

This last pair of publications, along with reports that the chromosome 11 marker was *not* linked with bipolar disorder in two other samples studied (33, 34), confirmed that bipolar illness exhibits nonallelic genetic heterogeneity (see the next section). Two recent studies (35, 36) that examined possible linkage between chromosome 5 markers and schizophrenia suggest that heterogeneity may also characterize that disorder. Research on other affective disorders is likely to yield similar evidence. Linkage studies will be central in differentiating subtypes of these illnesses, in defining their specific pathogenetic processes, and, ultimately, in refining treatment strategies.

Certain chromosomal abnormalities (e.g., Down's syndrome), biochemical abnormalities (e.g., Tay-Sachs disease), the presence of α -fetoprotein (an indicator of neural tube defect), and other predictors of severe illnesses have been identifiable in utero for several years through amniocentesis and, more recently, chorionic villus biopsy. Further technological advances (e.g., the polymerase chain reaction) now make it possible to amplify and analyze fetal DNA for the presence of known RFLPs as well. The result is that several other hereditary defects (e.g., sickle cell anemia [37]) may also be diagnosed in utero. In addition, the DNA of unaffected individuals with hereditary illness in their families can be examined for markers indicating that they "carry" the defective gene.

Recombinant DNA technology has major implications for treating hereditary disease in the future. The terms "recombinant DNA" and "gene splicing" refer to the fact that two DNA fragments with chemically complementary ends can, in the presence of the appropriate enzymes, be joined at will. The new, recombinant molecules can become the material for genetic engineering, by which the altered DNA associated with illness might be replaced with a normal sequence.

The first step toward genetic engineering, the cloning of normal human genes, has already been taken for dozens of genes. With the goal of eventually "curing" patients with systemic disease, genetics researchers are refining the process of inserting genes into bone marrow in animal systems. To cure individuals with CNS disease, it will be necessary to devise techniques for inserting a normal gene into an embryo (or into fetal tissue, which might then be transplanted intracerebrally), keeping the gene in place, and ensuring that it functions properly. Monumental though this enterprise is, work with one experimental model has already produced an encouraging result. A genetic "cure" was reported in 1987 (38) for neurologically impaired shiverer (*shi*) mice, which lack the normal capacity to produce myelin. A transgene coding for myelin basic protein was introduced into the mouse genome at a location apart from the *shi* locus. Animals resulting from the crossing of transgenic mice and *shi* mice now produced myelin, did not show the *shi* strain's characteristic tremor, and did not die prematurely, as *shi* mice typically do.

FUTURE DIRECTIONS IN PSYCHIATRIC GENETICS

The past decade has witnessed major advances in psychiatry, in particular, the refinement of disease subtypes, made possible in large part by more sophisticated biological characterization of disorders. From the study of phenomenologically defined subsets of patients—based on symptoms, age at onset, response to medication, coexistence of another disorder, and pattern of recurrence—new biological markers will emerge, providing new leads for linkage studies. Genetic research in turn will "feed back" information

that may either support or suggest modification of existing hypotheses about nosology and pathogenesis.

Meanwhile, molecular biology and statistical genetics are evolving steadily. Second-generation molecular markers such as variable number of tandem repeats (VNTRs) (39) and minisatellite DNA (40) promise to be significantly more polymorphic than conventional RFLPs. Such markers will be informative in most pedigrees—an important advantage in studying disorders for which large pedigrees are hard to find. Statistical genetics has advanced beyond the analysis of single markers linked with specific illnesses to multipoint linkage and interval mapping (41). These methods permit analysis of linkage to markers lying comparatively close to one another, with a substantial increase in statistical power. Simultaneous search, affected-sibling-pair analysis, and other statistical advances are expected to help substantially in the search for major disease loci.

Generally speaking, the next phase of research in psychiatric genetics can be envisioned as addressing several problems: etiologic heterogeneity, incomplete penetrance, variable expressivity, and pedigree limitations. The new methods may also shed light on the interaction between genetic vulnerability and environmental factors in pathogenesis.

Etiologic Heterogeneity

There is a growing body of evidence that several psychiatric illnesses—certainly, bipolar affective illness and, most probably, schizophrenia as well—constitute a spectrum of disorders, not a single entity. Such etiologic heterogeneity may result from, among other things, nonallelic genetic heterogeneity, phenocopies, or both.

Nonallelic genetic heterogeneity refers to the circumstance in which different genes are affected in different individuals. These genes interfere in a given developmental pathway at different points but ultimately lead to similar clinical manifestations. A varied etiologic basis has been proposed for bipolar disorder (31–34).

Phenocopies are nongenetic cases of an illness that present a clinical picture similar to that of a hereditary form. Separation of any nongenetic forms may be a particularly strong strategy. For example, there is a body of work indicating an excess of late-winter and early-spring births among patients with schizophrenia (42), which may reflect a season-related form of perinatal brain damage. If cases are grouped by season of birth, there is, in fact, a greater proportion of patients at low genetic risk for schizophrenia in the group born between January and April (58%) than in the group born during the rest of the year (14%) (43). Thus, the former group of cases might be separated out, and the remaining cases would likely be enriched for one or more genetic variants. Similarly, a recent study of major depression (17) found that cases in which onset occurred after age 30 were more likely to be pheno-

copies than were cases with earlier onset, which appear to be familial.

After nongenetic forms have been eliminated, linkage studies can determine whether different linked markers cosegregate with disease in the remaining pedigrees. If they do, as the Amish and Israeli studies indicate (31, 32), the finding will strengthen the evidence that those disorders are genetically distinct. The capacity to search for linkage to more than one marker at a time will greatly expedite this process. Until recently, it was possible to analyze a set of pedigrees for linkage to only one chromosomal region. If, for instance, the Amish and Israeli pedigrees had been tested together, linkages to chromosome 11 and the X chromosome, respectively, would have canceled each other out, with the false-negative conclusion that there was no single major gene effect. The availability of a complete linkage map of the human genome (41) brings into view the prospect of simultaneous, and much more efficient, search for suspected markers.

Incomplete Penetrance

Whether individuals with any given genetic variant will actually develop a corresponding disorder depends on the disorder's degree of penetrance, that is, the likelihood that the genetic abnormality will be expressed. Some disorders, characterized by age-dependent penetrance, do not fully manifest themselves until late in life, Alzheimer's disease being perhaps an extreme example (44).

In a study of schizophrenia that may be seen as illustrating incomplete penetrance (45), the offspring of monozygotic twins discordant for schizophrenia were compared. No significant difference in frequency of schizophrenia or of schizophrenia-like psychosis was found between the two groups. These results were corroborated in a follow-up study conducted 18 years later: among the original subjects, the age-corrected risk for schizophrenia in offspring of patients was 16%; in offspring of never affected monozygotic co-twins, the age-corrected risk was 16.8% (46). While such discordance might be attributable to phenocopies of illness in the affected twins, it is more likely that both twins are at genetic risk but that schizophrenia remains unexpressed in the unaffected twin.

Incomplete penetrance has been a stubborn obstacle to psychiatric genetic studies. However, innovations as well as adaptations in methods of data analysis have been developed to contend with it. The likelihood method for analysis of linkage has been modified to account for incomplete (e.g., age-dependent) penetrance (27). The affected-sibling-pair approach avoids the problem of incomplete penetrance by examining linkage only in clearly affected members of pedigrees.

A promising approach to the problem of penetrance is the identification of endophenotypes. An endophenotype is a biological abnormality that appears to represent a more immediate result of the hypothe-

sized genetic defect than does the clinical syndrome. Such an abnormality can be posited as a marker for hereditary vulnerability to the disorder and would, presumably, demonstrate greater penetrance (i.e., occur with greater frequency) than the illness itself. Accordingly, the feature might appear in a patient's unaffected relatives. In patients, only "trait" rather than "state" (i.e., enduring rather than episode- or treatment-related) features of illness would qualify as an endophenotype.

Studies of individuals at risk for alcoholism have yielded several possible endophenotypes for biological vulnerability. One report (47) described a neuroendocrine difference between children of alcoholics and control children that may be limited to males. In other research, individuals at high risk consistently showed reactions to alcohol that differed along several parameters, including EEG patterns, from those of low-risk subjects (48–50). This bimodal distribution of behavioral, neurophysiological, and neurochemical patterns of response may reflect discrete differences in several brain systems.

Other interesting findings have been published on panic disorder. Infusion with sodium lactate has been found to precipitate the physiological changes that occur during an acute panic attack (51, 52). There is also mounting evidence for abnormal respiratory physiology in a substantial percentage of panic patients (53). Positron emission tomography studies have shown asymmetrical cerebral blood flow in the parahippocampal gyri, during the resting state, of panic patients with a positive response to sodium lactate (54).

If the same chemical challenges and brain imaging studies were given to asymptomatic relatives of patients, with positive results, an endophenotype for panic disorder could be postulated. In searching for a Mendelian segregation pattern, one could test the findings against different models for intergenerational transmission, which might then help to define the disease phenotype for linkage studies.

Variable Expressivity

It has been proposed that dysfunctional smooth-pursuit eye movement may be an endophenotype of schizophrenia, since this neurophysiological abnormality has been reported in 60% of schizophrenic patients studied and in 55% of their first-degree relatives (55). However, dysfunctional smooth-pursuit eye movement might be an example of variable expressivity. If the same genetic abnormality produces different manifestations as a consequence of other aspects of the genetic context or of nongenetic probabilistic processes, it is characterized by variable expressivity. In numerous instances, patients with schizophrenia do not have deviant smooth-pursuit eye movement, but their nonschizophrenic relatives do. The postulated "latent trait" (56) may indeed reflect a pathogenic process in the brain that produces either schizophrenia, deviant smooth-pursuit eye movement, or both. But

there may be an important practical advantage in regarding deviant smooth-pursuit eye movement as a more common manifestation of the schizophrenia trait than is the clinical syndrome(s). Linkage studies using both clinically manifest schizophrenia *and* this biological marker to define the affected phenotype might be considerably more fruitful than those using clinical illness alone.

It has also been reported that major affective disorder and anorexia nervosa appear to cosegregate in families, with a significantly higher rate of major affective illness in relatives of anorexia patients than in relatives of control subjects (57). This finding suggests that anorexia may be a genetic variant of affective illness.

Pedigree Limitations

Pedigree information is more difficult to obtain for psychiatric genetic studies than for studies of many other types of illness. Families may be inaccessible, uncooperative, or relatively small. For example, individuals with schizophrenia may be more geographically mobile (58) and produce significantly fewer children than the general population. Moreover, people tend to choose marriage partners who are temperamentally (and often psychiatrically) similar to themselves. Such "assortative mating" leads to genetic combinations that contradict certain traditional assumptions, such as the independent segregation of genes, on which statistical analyses are based (59).

The problems posed by small family size, assortative mating, and genetic heterogeneity may be minimized by identifying and studying geographical isolates. The Amish study of bipolar disorder (31), the northern Swedish study of schizophrenia (60), and the Venezuelan study of Huntington's disease (30) all focused on such groups. Consanguineous marriages, as well as geographical isolation itself, minimizes the likelihood that the illness under study reflects more than one genetic variant.

Nature/Nurture

Innovative molecular and statistical techniques will also usher in a new era of inquiry into how hereditary liability interacts with environmental factors. Schizophrenia, the most notoriously elusive of psychiatric disorders believed to be genetically based, has been the object of many risk studies. Traditional methods took into consideration all offspring of patients (and patients' monozygotic twins, if any). Theoretically, then, as many as 50% of the subjects—if the gene for schizophrenia were a fully penetrant, dominant gene—could be expected to inherit it. A thorough search for early manifestations of illness among that many high-risk individuals would be very unwieldy.

However, assume that a genetic marker for any form of schizophrenia is found which lies within 5 cM of the disease gene. Any offspring with the marker would

have a 95% probability of having the illness as well. It would then be possible to compare such ultra-high-risk individuals with control subjects and to observe primary pathogenesis much more directly. A linked marker would also substantially help the search for endophenotypes. These, in turn, would permit more sophisticated linkage analyses.

If molecular and statistical genetics continue to progress at their present swift pace, many questions about the relationship between biological features of mental illness, genes, and the environment may be answered in the foreseeable future.

CLINICAL AND PUBLIC POLICY ISSUES

Arguably, psychiatrists are especially well equipped by their training to help people with the feelings and issues raised by hereditary illness, psychiatric or otherwise. The complexity and emotional impact of these situations are great; they are discussed in depth elsewhere (61). We outline some of these issues here in order to suggest both their range and the seriousness with which the profession must approach developments in genetics in the years ahead.

Ideally, clinicians should have a current working knowledge of genetic issues and advances. Among the matters of which psychiatrists should be aware are risk figures (empirical estimates of the risk of recurrence in families), established or likely modes of inheritance, diagnostic methods, and available treatments. Interpreting any genetic information to patients also requires considerable acumen. It is one thing to quote probabilities, another to formulate them in ways that will make sense to the individual patient and not do more harm than good to his or her mental health. A point worth emphasizing is that recognition of a genetic factor can, in some instances, free patients and their families from self-blame and some aspects of stigma.

Counseling issues vary with the nature of the disease. Bipolar disorders, for example, are not necessarily fatal, and effective treatments are available. Neither of these mitigating circumstances applies to Huntington's disease. Also, the degree of penetrance alters the burden of illness. Whereas a known carrier of Huntington's disease may reject the idea of having children because of the disease's severity and because the disease is fully penetrant, a carrier of bipolar disorder may be more inclined to raise a family. Age at onset is also a factor. The individual carrying a gene for Alzheimer's disease, which usually is not manifest until the seventh decade of life, faces one prospect; the person who may develop—or whose children may be at risk for—an illness that expresses itself clinically around ages 20–25 (e.g., schizophrenia) faces something entirely different. Another possible complication is genetic heterogeneity, of which a case in point is bipolar disorder. A marker pattern suggesting a genetic

vulnerability in one family might not be relevant to another.

The issues of whom to test diagnostically for genetic abnormalities, when to offer testing, and how to interpret results to patients are laden with ethical as well as psychotherapeutic problems. With a disorder such as Huntington's disease, the diagnosis of other family members, who may prefer not to know about it, is often "contained" in the diagnosis of an individual who does choose to be tested. There are difficulties at every turn in this scenario: the anguish of knowing, the anguish of being spared while a loved one is not, and the discovery that, for example, a decision not to bear children was in fact unnecessary. The time may come when employers or insurance companies will wish to make testing mandatory. Solid support, including crisis intervention, must be made available to meet the needs of persons under the extraordinarily stressful circumstances that testing may create. Certain analogous issues have arisen in the context of testing for the human immunodeficiency virus, notably the stigma attached to the diagnosis and the lack of effective treatment. Possibly, the challenges posed by the AIDS epidemic may suggest approaches to neuropsychiatric genetic testing.

In situations where the practitioner feels that he or she has insufficient expertise to offer genetic counseling, the patient should be referred to someone else, preferably to a psychiatrist specializing in these problems. An international directory of genetic services (62) is available; it gives the names of professionals specifically trained in behavioral or neuropsychiatric genetics.

During or after genetic counseling, psychiatrists will need all the sensitivity and expertise that they can bring to bear in helping people with the distress that genetic knowledge may cause them. A patient's grief or demoralization at receiving equivocal news about risk status may be difficult to distinguish from the onset of depressive illness. Moreover, the clinician must be attuned to early signs of illness in a person who is at risk but has previously been asymptomatic and must bear in mind that the clinical manifestations of hereditary neuropsychiatric illness vary among members of the same family as well as among families.

On the one hand, the availability of predictive tests for mental illness could add serious new problems having to do with health benefits, employment, and stigma to those already faced by psychiatric patients and their families. On the other hand, wider recognition of the biological basis for mental illnesses may allow these illnesses, finally, to be seen as similar to other medical problems. Why is bipolar affective disorder poorly covered by insurance, for example, when its neighbors on chromosome 11 and the X chromosome—diabetes mellitus and hemophilia, respectively—are fully covered? Equal support and compassion would do much to relieve the burden for people at risk and for their family members.

CONCLUSIONS

Molecular genetics is as exciting as any science in medicine today, notably in its impact on psychiatry. As we discover more about individuals' genetic endowment, we can also learn more about how they differentially respond to environmental influences and we can use what we learn to help them. The technology available now could hardly have been dreamed of 10 years ago. The therapies and preventive strategies that are emerging from it go to the very root of illness, and progress continues at a rate that encourages high hopes for the future.

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Splitting in Hospital Treatment

Glen O. Gabbard, M.D.

Splitting is a concept that is used in a variety of ways to describe several different phenomena commonly seen in hospital treatment. As defined in this paper, it should be reserved for situations in which intrapsychic and interpersonal splitting occur simultaneously, recreating the patient's internal object world in the milieu. Through projective identification, staff members unconsciously identify with projected aspects of the patient and behave accordingly. A clearer conceptual understanding of splitting in the hospital allows for its differentiation from common variants of splitting and for the development of strategies to manage splitting.
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The unfortunate fate of many fashionable psychiatric terms is to be misused and overused. Just such a fate has befallen the term "splitting." Along with the increased sophistication over the last two decades in the hospital treatment of patients suffering from borderline personality disorder, there has been a corresponding increase in the jargon associated with that disorder. One commonly hears nurses, activities therapists, psychiatrists, and other hospital staff members refer to a patient as a "splitter." This label is almost invariably applied in a pejorative manner, as though the patient were a hardened criminal. Similarly, when a disagreement occurs between two treaters involved in the hospitalization of a patient with borderline personality disorder, one is likely to observe to the other: "The patient is splitting us." Such glib pronouncements may at once ease the tension between the parties and appear to explain the disagreement by "blaming" the patient. However, the use of the term may or may not be appropriate in the context in which it is invoked.

The broad application of the concept of splitting to a variety of situations has threatened to rob the term of its specific meaning. It has become something of a wastebasket term that serves as a repository for a wide range of behaviors and experiences involving various forms of manipulation, transference-countertransfer-

ence phenomena, and virtually all varieties of disagreements among staff members. This lack of clarity has weakened a concept that can be of extraordinary value in hospital treatment. In this paper I will propose a more specific conceptualization of splitting, one that differentiates the term from other clinical phenomena with which it may be confused.

THE CONCEPT OF SPLITTING

A number of authors (1-4) have commented on the wide and varied usage of the splitting concept. The multiple connotations of the term, stemming from diverse theoretical underpinnings, have even led some to advocate abandonment of the term (2). For the most part, however, there is a general consensus that the key notion involves maintaining contradictory aspects of intrapsychic experience separate from one another. Moreover, most authors would agree that splitting is both a normal developmental mode of organizing the infant's intrapsychic experience and a defense mechanism that ultimately arises from this mode.

Although Freud seemed to prefer the defense of repression to that of splitting, references to splitting of the ego are scattered throughout his papers (5). Particularly toward the latter part of his career, references to the phenomenon became increasingly common. In his 1927 paper on fetishism (6), he described two states of mind coexisting side by side despite the fact that each was associated with an idea that seemed incompatible with the other. By the time of his death, Freud had become convinced that splitting was a virtually universal feature of human psychopathology which derived from infancy and persisted in neurotic as well as in psychotic and fetishist patients (7, 8).

Although classical analysts for the most part failed to see the value of Freud's concept, Melanie Klein (9) viewed splitting as essential to understanding the infant's early anxieties. Convinced that life constituted a struggle between the life and death instincts, Klein viewed splitting as the cornerstone of emotional survival in the first several months of life. Splitting allows the infant to separate good from bad, pleasure from unpleasure, and love from hate to preserve positively colored experiences, affects, self-representations, and object representations in a safely isolated mental compartment, free from contamination by their negative counterparts.

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One can best illustrate the developmental basis of splitting by examining the infant's feeding experience. A prototype of loving, positive experience is formed during periods when the infant is nursing (10). This prototype includes a positive experience of the self (the nursing infant), a positive experience of the object (the attentive, caretaking mother), and a positive affective experience (pleasure, satiation). When hunger returns and the infant's mother is not immediately available, a prototype of negative experience occurs, including a negative experience of the self (the frustrated, demanding infant), an inattentive, frustrating object (the unavailable mother), and a negative affective experience of anger and perhaps terror. Indeed, the fundamental source of splitting lies in the fact that the infant's mother is both nurturing and frustrating (11). Ultimately, these two experiences are internalized as two opposing sets of object relationships consisting of a self-representation, an object representation, and an affect linking the two (12-17).

The internalization of the infant's mother, usually referred to as introjection (18), begins with the physical sensations associated with the presence of the mother during nursing but does not become meaningful until a boundary between inner and outer has developed. Isolated images of the mother gradually coalesce into an enduring mental representation of her around the 16th month of life (19). At the same time an enduring self-representation forms, first as a body representation and later as a compilation of sensations and experiences perceived as belonging to the infant. Representations in these early stages are necessarily rudimentary because of the limitations of the cognitive and perceptual faculties of the infant (3).

The positively colored or "good" object representation begins as a hallucinatory wish fulfillment growing out of the hungry infant's longing for the mother (18) and is later transformed into an internal presence as the infant's cognitive-perceptual apparatus develops. A major motivating force in the introjection of the positive, loving aspects of the mother seems to be the infant's fear of losing the mother (18). The reasons for the introjection or "taking in" of the negative, "bad" aspects of the mother are more complex. Possible motivating factors include the fantasy of controlling the object by containing it within oneself (20), gaining a sense of mastery through repeated traumatic experiences with the object (18), and a preference for a bad object over no object at all (18). Clinical experience suggests that intense attachment to an internalized hostile object may also be connected with a yearning for a more positive relationship with the object (21). Furthermore, the object that has been introjected does not necessarily correlate with the real external object. For example, a mother who is unavailable to feed her infant on demand may simply be occupied with an older sibling, even though she is experienced and introjected by the infant as hostile, rejecting, and unavailable.

Even before the self- and object representations are firmly established, one can observe forerunners of

splitting. The good, loving experiences are kept separate from the bad, terrifying experiences to preserve a safe feeding experience. Nursing would be disrupted if negative images of the unavailable mother were allowed to intrude. As boundaries between the inside and outside develop and images coalesce into representations, negative aspects of the self- and object representations threaten to destroy the positive aspects. Hence, splitting is maintained as an active defensive process to keep good separated from bad (22). The introjects resulting from this process are often referred to as "part objects" as a way of acknowledging that they lack the "whole" quality of more mature introjects, which are characterized by a mixture of positive and negative qualities.

Splitting is enhanced by projection, which involves unconsciously attributing the bad qualities to a person in the environment while all good qualities remain within, thus effecting a further separation of the polarized aspects. Positive or good attributes of the self- or object representations may also be projected to keep them at a safe distance from the bad within (20). In this manner splitting serves to bring order to the infant's early chaotic experience (1, 3, 4, 23). Furthermore, by managing danger in a way that is necessary for the infant's emotional survival, it constitutes the original paradigm of intrapsychic defense (3, 23).

Splitting is best understood as a universal mechanism growing out of normal development. Although it may operate across a broad spectrum of diagnostic categories (4, 24, 25), much of the term's popularity is derived from Kernberg's notion that splitting is the key defensive operation involved in the borderline personality disorder (22, 26). He described splitting as an active process of keeping contradictory introjects and affects separate from one another, resulting in the following clinical manifestations: 1) alternating expression of contradictory behaviors and attitudes, which the patient regards with lack of concern and bland denial, 2) selective lack of impulse control, 3) the compartmentalization of all persons in the patient's environment into all good and all bad camps, with frequent oscillations between camps for a given individual, and 4) the coexistence of contradictory self-representations that alternate in their dominance from day to day and from hour to hour.

The studies of normal and pathological mother-infant dyads of Mahler et al. (27) provide some observational data to bolster Kernberg's view that the developmental fixation in patients with borderline personality disorder occurs at a point in childhood before the integration of good and bad part objects into an ambivalently regarded whole object. Mahler and her colleagues supplied empirical evidence to suggest that such integration does not occur until the child achieves object constancy at the age of 2½ or 3 years. Mahler reasoned that the intense separation anxiety typical of the patient with borderline personality disorder is connected to this failure of object constancy, which leaves the patient without an integrated whole

object representation that can provide soothing functions in the absence of an actual parent.

A number of authors (9, 16, 17, 22, 23, 26, 28–30) have commented on the intimate relationship between splitting and projective identification. Ogden (23) noted that when an infant's positive view of the mother is threatened by a diametrically opposed perception, the latter can be projected externally as a way of separating the endangering object representation from the endangered one. In this manner, projective identification develops as an interpersonal elaboration of the intrapsychic splitting process. Ogden (30) saw projective identification as unfolding in three steps: 1) The patient projects an object or self-representation onto the treater. 2) The treater unconsciously identifies with that which is projected and begins to feel and/or behave accordingly as a result of interpersonal pressure exerted by the patient. This reaction has been termed "projective counteridentification" (31). 3) The projected material is "psychologically processed" by the treater and returned in modified form to the patient through reintroduction.

The interpersonal element inherent in Ogden's definition of projective identification derives from Bion's conceptualization of the therapist as a container for the projections of the patient (32), much as the mother contains the projections of her infant. Other authors (5, 33–36) have disagreed with the broadening of the definition to include a particular response of the treater to the projected aspects of the patient. They preferred a narrower view of projective identification as an intrapsychic defense that may or may not result in a reciprocal response from the clinician. Grotstein (5), for example, shared Kernberg's view (34) that the identification occurs within the projector rather than within the target of the projection. By maintaining this empathic bond or identification with that which has been projected, the projector has the fantasy of control over the projected material. Most authors would agree that this element of control is central to the concept. Sandler (35) noted, "What one wants to get rid of in oneself can be disposed of by projective identification, and through controlling the object one can then gain the unconscious illusion that one is controlling the unwanted and projected aspect of the self" (p. 20). Ogden's three-step formulation (30) is completely in keeping with this notion except that he viewed the identification as occurring in both the treater and the patient rather than in the projector-patient alone. Because splitting and projective identification in the hospital setting have a powerful interpersonal dimension, I will preserve Ogden's broadened use of projective identification for the purposes of this communication.

In summary, splitting and projective identification are two interrelated mechanisms that provide a basic mode of organizing experience from early in life. The loved mother can be separated from the feared and hated mother, while the hating self of the infant can be compartmentalized apart from the loving self. These mechanisms allow the infant to feed safely without

fear of intrusion from negative self- or object representations. These operations prevent the good from being destroyed by the bad and provide an opportunity for the infant to experience disturbing aspects of the self and others at a distance until he or she is more psychologically ready for the task of integration.

SPLITTING IN THE HOSPITAL

Splitting in the hospital has been well described in a number of papers on the intense countertransference evoked by treatment-resistant patients with borderline personality disorder (17, 37, 38). Staff members find themselves assuming highly polarized positions and defending those positions against one another with a vehemence that is out of proportion to the importance of the issue. The patient has presented one self-representation to one group of treaters and another self-representation to another group of treaters (17, 38–40). Through projective identification, each self-representation evokes a corresponding reaction in the treater that can be understood as an unconscious identification with the projected internal object of the patient. The transference-countertransference paradigm produced by one self-object constellation may be dramatically different from that produced by another. This discrepancy may first manifest itself in a staff meeting where the patient is being discussed. One group of staff members becomes puzzled by the description they are hearing and may ask, "Are we talking about the same patient?"

Full-blown splitting of this variety illustrates the time-honored notion that the patient recapitulates his or her internal object world in the hospital milieu. Various treaters become unconsciously identified with the patient's various internal objects and play out roles in a drama that is written by the patient's unconscious. Moreover, because of the element of control inherent in projective identification, there is often an obligatory quality to the treaters' responses. They feel compelled to behave "like someone else." If projective identification were not involved, the purely intrapsychic splitting that would result would cause little disturbance in the staff group. Nor would the staff group view the process as an example of splitting, since they would probably not feel polarized and angry toward one another.

The splitting that occurs in hospital treatment represents a special case where both intrapsychic and interpersonal splitting are taking place simultaneously (36). The interpersonal aspects of splitting that occur in staff groups clearly parallel the intrapsychic splitting occurring in the patient. Projective identification is the vehicle that converts intrapsychic splitting into interpersonal splitting.

Staff members who are singled out as recipients of projected internal objects of the patient are not randomly selected. More often than not, patients with borderline personality disorder have an uncanny ability to detect preexisting latent conflict among various

staff members, and their projections may be guided accordingly. A vignette from an actual case illustrates this pattern.

Case 1. Ms. A, a 26-year-old patient with borderline personality disorder, was admitted to the hospital by her psychotherapist, Dr. B. At admission, she was in a suicidal crisis. Ten days after her admission, while she was still voicing suicidal ideation, Dr. B approached Mr. C, the head nurse of the unit, and said he would like to drive Ms. A to the local college campus so she could register for the semester. Mr. C replied that, according to hospital policy, patients who are on suicide precautions may not leave the unit. He suggested that Dr. B might want to attend a unit staff meeting to discuss further the management of the patient. When Mr. C explained to Ms. A that she could not leave the unit to register, she was enraged with Mr. C and told him he was a tyrant who had no regard for the individual needs of patients. She contrasted him with Dr. B, whom she idealized by saying that among all the staff members associated with her treatment, he was "the only one who understands me." At the ensuing staff meeting, a heated argument developed between Dr. B and Mr. C, who acted as a spokesperson for the unit staff. In the midst of this clash, Mr. C told Dr. B that the latter was well-known for his contempt toward hospital policies and for his propensity to treat patients as "special." As a rebuttal to that accusation, Dr. B informed Mr. C that of all the nurses in the hospital, he was the most rigid and punitive by reputation.

This example demonstrates how splitting and projective identification do not occur in a vacuum. Ms. A clearly picked out individuals who conveniently fit the internal object relationship paradigms assigned to them. As several authors (28, 29, 38) have noted, there is often a kernel of reality in the assignment of internal object projections to staff members. This vignette also reflects Burnham's observation that the cleavage is usually between those treaters who emphasize the administrative frame of reference (what is good for the group) versus those who emphasize an individualistic frame of reference based on what is good for an individual patient (38). Finally, although all treaters are at risk for involvement in splits, the pattern described in this vignette is perhaps the most common variety found in the treatment of the patient with borderline personality disorder: the psychotherapist is viewed as an idealized figure while the unit staff are devalued as insensitive and punitive. Another typical feature of this arrangement is that the patient may omit information deriving from day-to-day unit activities in his or her psychotherapy sessions and focus exclusively on childhood memories and transference material (28, 41). The psychotherapist then has no awareness of the problematic interactions on the unit and is caught by surprise when nursing staff bring them to his or her attention.

Adler (28) noted that the hospital staff may actually exclude the psychotherapist from the process of treatment planning as a result of this form of splitting. In this manner the unit staff may consolidate the alliance with one another by projecting badness and incompe-

tence outside the unit group onto the psychotherapist. If this process goes on unchecked, it becomes impossible for the unit staff and the psychotherapist to reconcile their differences and meet each other halfway. Just like the patient's internal objects, they cannot be integrated. The regressive power of groups is well-known and may result in the use of splitting and projective identification in otherwise well-integrated professionals (41-43).

When a staff group reaches this point of fragmentation, all too often the patient is blamed for attempting to "divide and conquer" (44). What is often forgotten under these circumstances is that splitting is an unconscious process that the patient uses automatically to maintain his or her emotional survival. We do not generally blame patients for other defense mechanisms. The unique issue in splitting seems to be the perception by treaters that the patient is being consciously and maliciously destructive. An empathic frame of reference is useful to remind staff members that splitting is the patient's attempt to ward off destructiveness and protect himself or herself from being destroyed by it.

To summarize, splitting in hospital treatment involves four primary features: 1) The process occurs at an unconscious level. 2) The patient perceives different staff members in dramatically different ways, based on projections of the patient's internal object representations, and treats each staff member differentially according to those projections. 3) Staff members react to the patient, through projective identification, as though they actually were the projected aspects of the patient. 4) As a result, treaters assume highly polarized positions in staff discussions about the patient and defend those positions with extraordinary vehemence.

VARIANTS OF SPLITTING

The features enumerated here serve to distinguish splitting involving both intrapsychic and interpersonal dimensions from variants that also occur commonly in hospital treatment.

Intrapsychic Splitting

The splitting process already described has a powerful interpersonal aspect due to the associated projective identification process. However, when splitting occurs without projective identification, it may remain a purely intrapsychic phenomenon.

Case 2. Mr. D, a 44-year-old attorney, presented an assertive hypermasculine presence in the courtroom. At night, however, he liked to dress in women's clothing and think of himself as an elegant lady. These two contradictory self-representations presented little conflict for the patient, who regarded them with bland denial by saying simply, "I'm a multifaceted person." Both of these dimensions appeared in his hospital treatment, but neither produced intense countertransference reactions in the treaters.

Some patients with borderline personality disorder present alternating self-representations to different staff members, but they simply do not evoke corresponding object responses. Hence, no significant interpersonal dimension is activated, and staff members are not likely to engage in vociferous disagreements of the kind seen in splitting associated with projective identification.

Manipulation

Patients with borderline personality disorder are frequently referred to as manipulators, and their manipulative behavior is frequently called splitting. Because patients who suffer from borderline pathology live in constant dread of abandonment, they often display an inordinate need to control the behavior of others, thereby reassuring themselves that they are not as vulnerable to the whims of those around them. Such patients will often go from one staff member to another trying to get the attention they feel they need. Similarly, they may make mild self-destructive gestures or engage in other acting-out behaviors that are designed to assure that treaters will pay attention to them. To elicit the response they wish to receive, they will flatter, cajole, coax, seduce, or otherwise coerce the treatment staff.

Case 3. Ms. E, a 20-year-old college student, felt that no one on the hospital treatment staff was paying sufficient attention to her. In group meetings she would assert that all the other patients on the team received more "staff time" than she did. As a way of extracting more interaction time from the nursing staff, she would frequently bring up somatic complaints. One evening she went to four different nurses with the same physical complaint. When she did not receive the attention she desired from one nurse, she would seek out another nurse, hoping that this one would satisfy her needs. After going through all four staff members without success, she gave up and went to her room, where it was reported that she was sulking. The next day in the staff meeting, one of the nurses reported that she felt Ms. E was "splitting" staff by seeking out other opinions when she wasn't getting what she wanted from the first nurse she approached.

Although this behavior was called splitting, each staff member, in fact, was viewed and treated in the same manner. Moreover, the process was operating at a largely conscious level (Ms. E later admitted that she was using the complaint to get attention). Finally, although there was some projective identification, as evidenced by the anger of the nursing staff at the patient, the nursing staff did not feel split into different camps as a result of differing identifications, nor did they have any substantial disagreement about what the patient was doing. On the contrary, there was considerable unanimity regarding how the patient was perceived. In other words, one internal object representation was consistently being projected in all interactions.

Unfortunately, when a patient is seen as manipulative, he or she is often blamed for the behavior rather

than viewed in an empathic context. The knowledge that Ms. E had a conscious wish for attention should not have obscured the fact that an unconscious internal object relationship was being played out as well. An aspect of the self was yearning for a particular object response. Adler (28) pointed out that some manipulation is largely unconscious and has an adaptive function in that it keeps the patient from being alone. If the treatment staff keep this perspective in mind, they can gain greater mastery over countertransference reactions.

Lying

Although linked in some ways to manipulation, lying is more consciously exploitative and ruthless in its intent. Patients with borderline personality disorder with prominent antisocial features are obviously more likely to engage in deception, and their dishonesty presents a whole array of treatment problems. Since lying can often set one staff member against another, this behavior is often erroneously viewed as splitting.

Case 4. Mr. F, a 29-year-old drug abuser, was in long-term hospital treatment for a variety of problems stemming from dysfunction in relationships and job situations and failure to respond to short-term interventions designed to help him with his drug abuse. Part of the structure established on the unit was for him to open all letters in front of staff members because he had been receiving drugs through the mail. One evening when Mr. F received his mail, he informed Ms. G, a nurse who was preparing to observe Mr. F's letter opening, that it was no longer necessary for him to follow this element of his structure because his doctor had told him that such observation had outlived its usefulness. The next day Ms. G angrily confronted Mr. F's doctor and told him that such decisions should be discussed with all staff members in team meetings. She went on to say that she resented the doctor's unilateral decision making on this issue because she felt it was still necessary. Mr. F's doctor categorically denied that he had made any such statement to Mr. F. When the doctor and Ms. G went to Mr. F together and confronted him, the patient acknowledged that he had lied.

Although lying may turn staff members against one another, the cleavage does not grow out of the patient's alternating self-representations presented differentially to different staff members. The process is conscious and is far more malicious than the unconscious splitting process.

Staff Disagreement

All disagreements among staff members on a treatment team are not the result of splitting. Staff members working on a hospital unit will have a variety of different treatment philosophies regarding such matters as the use of structure, limit setting, gratification versus frustration of transference wishes, and the optimal level of staff control versus patient autonomy, to name just a few. Although these preexisting differences may serve as the nidus for splitting maneuvers by the pa-

tient with borderline personality disorder, there are many other instances in which staff members simply disagree because of differing philosophies.

It is a common occurrence in staff discussions for the patient to be blamed for these philosophical disagreements when one member of the discussion notes, "The patient must be splitting us. This says more about the patient than it does about us." This kind of statement lets the treaters off the hook. They do not have to attempt to resolve their differences. Instead, they can talk about the patient's tendency to engage in splitting.

The differentiation of staff disagreement from splitting is complex. The intensity with which positions are defended may be a useful index of the presence of splitting. When mere philosophical differences are present, one party usually retains some ability to listen to the other party and some empathic appreciation for the differing point of view. In the throes of splitting and projective identification, however, each party has become so polarized that there is no ability to see any value at all in the opposition, and the discussion frequently deteriorates into personal attacks.

This index is not foolproof, however, since group dynamics may result in splitting and polarization independent of the influence of the patient. These phenomena are particularly likely to occur in instances where the work task of the staff group becomes unclear or derailed and where there is a general feeling of demoralization among staff members (43). Differentiation of these group phenomena from patient-induced polarization may be possible by determining if the group differences occur along lines that parallel the patient's internal object world.

THE MANAGEMENT OF SPLITTING

Any discussion of how to manage splitting in hospital treatment must begin with Burnham's caveat that the complete prevention of splitting is neither possible nor desirable (38). As is the case with other defense mechanisms, splitting provides a safety valve that protects the patient from what is perceived as overwhelming danger. It is a process that will develop regardless of what preventive measures are implemented. The essential point here is that splitting must be continuously monitored by treatment staff to prevent it from destroying the patient's treatment, devastating the morale of the staff, and irreparably damaging certain interstaff relationships. Cases of serious psychiatric morbidity and staff resignations have resulted from such situations (37, 38).

The importance of education cannot be overemphasized. All mental health professionals working with hospitalized patients should be thoroughly conversant with the concept of splitting and its variants. If unit staff members cannot recognize splitting when it develops, the management of the situation may be hopeless. Clinical directors of psychiatric units must establish a cultural norm in which countertransference

feelings are viewed as an acceptable part of the treatment process and as containing valuable information about the patient (17). In discussions of countertransference, staff can be encouraged to work toward containing projected aspects of the patient rather than acting on them. Intense feelings toward patients should be viewed as useful material for discussion and supervision rather than forbidden reactions that must be concealed from one's supervisor. The mechanism of splitting can be explained to unit staff members so that they can avoid exploiting a split by accepting idealization and colluding with the devaluation of other staff members (29, 45). Monitoring of countertransference tendencies of staff members to project aspects of themselves onto the patient is also crucial.

Education is only a beginning, however. Regular and frequent staff meetings that include the patient's psychotherapist should be a part of the weekly routine of the psychiatric unit. A spirit of open communication about differences should be established and monitored by the staff. More than 30 years ago Stanton and Schwartz (46) persuasively demonstrated the prophylactic value of ferreting out covert staff disagreements and making them overt. Psychotherapists must view themselves as part of the treatment team and ally themselves with administrative decisions made by the unit team (28). Rigid adherence to concerns about confidentiality may feed right into the patient's splitting tendencies.

One major goal in the treatment of patients with borderline personality disorder is the integration of split self- and object representations. Although interpretation of the splitting mechanism is useful in helping patients achieve more moderated and realistic views of themselves and others, it is rarely sufficient to mend the cleavage that occurs at the group level in the hospital. Interpretations to the patient are best viewed as adjuncts to other interventions at the level of staff interactions. Corresponding to the psychotherapist's approach to the internal world of the patient, integration and moderation of the external objects are the goals of intervention at the staff level.

To this end, it is often useful to have a joint meeting of the staff member identified with the bad object, the treater identified with the good object, and the patient and have the three frankly discuss the patient's perception of what is going on. This arrangement makes it more difficult for the patient to maintain his or her polarized views; he or she sees both treaters acting human and reasonable. Moreover, treaters ordinarily become less polarized and move toward middle ground when they are faced with this situation. The very separateness demanded by the splitting mechanism is undermined. Although this may temporarily increase the patient's anxiety, the message is also conveyed that negative feelings can be contained within interpersonal relationships without disastrous consequences.

When the situation is so emotionally charged that the participants are not willing to meet, an objective consultant can be brought in as a mediator in the dis-

cussion (17). He or she can perform the role of an observing ego for the group and thereby encourage those individuals involved with the splitting to identify with that function, much as Shapiro et al. (29) described the function of the psychotherapist when meeting with adolescents with borderline personality disorder and their families.

These meetings presuppose a recognition by all parties that a splitting process is going on. Such acknowledgment constitutes a major step toward successful management of the splitting. Ordinarily, there is considerable reluctance on the part of staff members to see themselves as involved in splitting. When a special meeting is called to discuss the staff dynamics surrounding a particular patient, there may be strong resistance on the part of treaters because they feel that such a meeting will make the patient too special (38). If the patient's psychotherapist is involved in the split, he or she may be willing to attend the staff meeting but will come with a different agenda. Especially if he or she is idealized by the patient, the therapist is likely to assume the condescending position of educating the staff about their countertransference reactions and about the dynamics of the patient so they will understand the patient as well as the psychotherapist does. The implicit message of the psychotherapist in this situation is that by understanding the patient, the unit staff will stop blaming the patient. Rather than seeing the staff meeting as a productive way to discuss a splitting process, the psychotherapist's view is that he or she is right while everyone else is wrong. Being idealized may be so gratifying that the therapist does not wish to examine the idealization (47) and consider it a part of a defensive process in the patient. This approach will, of course, infuriate the unit staff even further and widen the split.

When a staff meeting is called to discuss potential splitting, the parties certainly should approach one another with the assumption that each is a reasonable and competent clinician who cares about the patient's welfare. When this approach works, the group feels that each staff member has brought a piece of the puzzle so that the whole is more clearly seen (38). However, some splits seem irreparable; just as the internal objects of the patient cannot be integrated, neither can the external objects reconcile with one another. If the therapist is cast in the role of the devalued object, such stalemates occasionally end with the unit staff recommending a new therapist (28).

The earlier the process is discovered, the less entrenched it will be and the more amenable to change. Certain warning signals should be continuously monitored in staff meetings: 1) when a treater is uncharacteristically punitive toward a patient, 2) when a treater is unusually indulgent, 3) when one treater repeatedly defends a patient against critical comments from other staff members, and 4) when a staff member feels that only he or she can understand the patient.

When staff members can swallow their pride and accept that they may be involved in an unconscious

identification with projected aspects of the patient, they can begin to empathize with other staff members' feelings and perspectives. This willingness to consider someone else's point of view can lead to collaborative work on behalf of the patient that results in marked improvement in the splitting process. The patient's internal split often begins to mend at the same time the staff's external cleavage heals (17). These parallel developments may be understood as the third step of projective identification—the previously split-off and projected object representations of the patient are contained and modified by the treaters and then reintroduced in modified form by the patient in a meaningful interpersonal context. By approaching their own differences in good faith, staff members provide an atmosphere in the milieu where good experiences predominate over bad ones, an essential condition to facilitate the integration of love and hate in the patient.

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Postcardiotomy Delirium: Conclusions After 25 Years?

Lawrence W. Smith, B.A., and Joel E. Dimsdale, M.D.

Although postcardiotomy delirium has been studied widely, there are few data about the current prevalence, compared to that reported in the late 1960s. There have been few efforts to replicate early observations. The authors review the literature using meta-analysis to combine the results of 44 studies. They examined the relationships between postcardiotomy delirium and 28 hypothesized risk variables. The prevalence of postcardiotomy delirium has remained fairly constant over time at 32%. There was no difference in the total prevalence of postcardiotomy delirium reported in studies that used interviews versus chart reviews. Sex, previous psychiatric illness, intelligence, and time on bypass failed to correlate with postcardiotomy delirium, and age correlated with it only slightly. Correlation coefficients of more than 0.30 were found only for noncongenital heart disease and postoperative EEG abnormality. Preoperative psychiatric intervention had the highest correlation with postcardiotomy delirium ($r = -0.60$).

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Since the introduction of open-heart surgery in the mid 1950s, physicians and hospital staff have noticed postoperative psychiatric complications in a significant number of their open-heart surgery patients. These complications, which vary from mild disorientation to hallucinations or paranoid delusions, have come to be classified as postcardiotomy delirium. The etiology of postcardiotomy delirium has been sought by numerous researchers over the years. Unfortunately, the results of the research have been conflicting and have failed to reveal reliable predictors or risk factors for postcardiotomy delirium. Despite the confusion and conflicting findings that characterize the literature on postcardiotomy delirium, some researchers (1-7) have reported their clinical impression that the incidence of the disorder has declined since the early

1960s, possibly due to improved surgical technique and a decreased amount of time that patients are now maintained on cardiopulmonary bypass.

In an effort to determine whether the reported prevalence of postcardiotomy delirium has indeed declined over the years and to find the factor or factors that may be responsible for such a decline, we reviewed the literature comprehensively by using meta-analysis (8, 9) to combine the results of a number of studies. Because meta-analysis is a technique for quantitatively summarizing data across reported studies, the conclusions derived from meta-analysis are dependent on the quality of reported studies, the frequency of replication of these studies, and clearly articulated decision rules applied by the reviewers in evaluating such studies.

METHOD

Forty-four research studies were analyzed (1, 2, 4, 5, 10-49). English language articles published in a variety of journals between 1963 and 1987 were used. A MEDLARS search, our reprint files, and correspondence with other researchers aided us in locating reference citations, which focused on psychiatric symptoms following open-heart surgery on adult patients.

Because these studies used diverse methods for assessing and classifying the psychiatric disturbances following open-heart surgery, we classified the various clinical presentations of postcardiotomy delirium into three groups. Group 1 included symptoms of disorientation to place or time; group 2 consisted of perceptual illusions, failure to recognize family or friends, or disorientation to identity; and group 3 included hallucinations, paranoid ideation, or agitation. In most of the studies the symptoms of delirium were described in sufficient detail to permit such classification. Some studies, however, mentioned only the fact that a certain percentage of the subjects became delirious, without describing the delirium; these cases were excluded from analyses of the qualitative manifestation of delirium but were included in analyses of the overall prevalence of delirium.

A number of researchers have commented on the fact that the method of determining the presence of delirium, i.e., by interview and observation or by review of patient charts, may yield differing frequencies of postcardiotomy delirium in the literature (10, 13, 50, 51). Thus, we also explicitly examined the preva-

Received Dec. 14, 1987; revision received Aug. 15, 1988; accepted Sept. 22, 1988. From the Department of Psychiatry, University of California, San Diego; and the Department of Psychology, San Diego State University. Address reprint requests to Dr. Dimsdale, Department of Psychiatry, University of California, San Diego (T-004), La Jolla, CA 92093-0804.

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lence of postcardiotomy delirium as revealed by both methods of case finding.

Meta-analysis permits quantitative estimation of a population correlation (ρ) by using the sample correlations (r) from a collection of independent studies. If specific values of r are not reported, estimates of ρ can be made using the "vote-count" method (8). The vote-count method is appropriate for our analyses because the articles reviewed generally report only the presence of relationships (positive or negative), without specifying r values. Many of the risk factors of interest in this review were addressed by as few as two or three studies. As a result, the estimates of ρ based on only a few studies should be considered rough, in that they carry with them relatively large confidence intervals. Despite this limitation, the rationale for our use of the vote-count method is simply to synthesize results and to highlight robust relationships found in studies that many times did not provide sufficient quantitative detail for meta-analytic study beyond the vote-count technique.

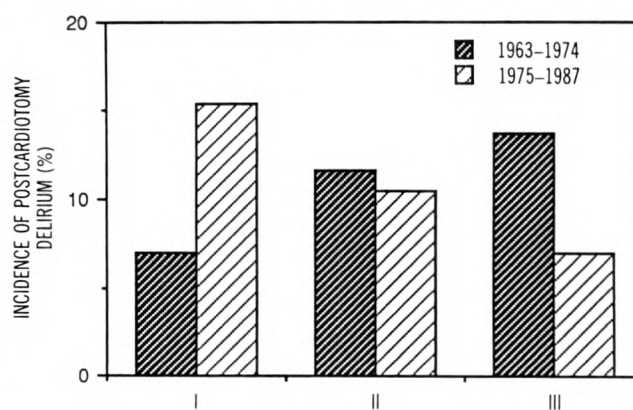
The vote-count procedure involves counting the number of studies that report a positive relation between each predictor variable and postcardiotomy delirium. The proportion of positive studies (U) to the total number of studies (k) that address a particular variable is then calculated. This proportion (U/k) is the probability that a correlation coefficient from a sample of size N will be positive when the population correlation coefficient is ρ . For example, if six of seven studies were to report positive associations between hematocrit and postcardiotomy delirium, then $U/k = 6/7 = 0.86$. This is the probability that a study will find a significant positive association between hematocrit and postcardiotomy delirium, given some true population correlation coefficient (ρ). By incorporating U/k with a weighting factor based on sample size, one can obtain an estimate of the population correlation coefficient (or ρ) (52). Because the sample sizes of our reviewed studies varied, we used the square mean root as our approximation for the average sample size (8). We extracted ρ values corresponding to our obtained probability values and sample sizes (8). These ρ values are the estimated population correlation coefficients reported in this paper. Meta-analysis uses both effect strength and sample size in its estimates of ρ values.

FINDINGS

Prevalence

According to our review the total prevalence of postcardiotomy delirium during the years 1963–1974 and 1975–1987 was 32.41 and 32.95%, respectively. It is clear that the reported total prevalence of postcardiotomy delirium has not declined since the 1960s but has remained fairly constant across the 25 years ($\chi^2 = 1.14$,

FIGURE 1. Clinical Presentation of Postcardiotomy Delirium^a



^aI=disorientation to place or time; II=perceptual illusions, failure to recognize family/friends, or disorientation to identity; III=hallucinations, paranoid ideation, or agitation.

$df = 1$, n.s.). For more detail, figure 1 shows the prevalence of postcardiotomy delirium for the various clinical presentations described earlier. A chi-square test in this case indicated that the distribution of types of symptoms differed significantly in the two blocks of years ($\chi^2 = 58.14$, $df = 2$, $p < 0.01$). More cases were categorized into group 3 (hallucinations, paranoid ideation, or agitation) for the early years 1963–1974 than for the later years 1975–1987. For the more recent years (1975–1987), more cases fell into group 1 (disorientation to place or time).

Interestingly, the overall prevalence of postcardiotomy delirium was unaffected by method of diagnosis, i.e., interview or chart review ($\chi^2 = 0.15$, $df = 1$, n.s.). For the particular presentations of postcardiotomy delirium, however, the interview was significantly more sensitive to group 1 symptoms than were chart reviews ($\chi^2 = 19.21$, $df = 1$, $p < 0.01$).

Demographic and Psychosocial History Variables

Table 1 lists demographic and psychosocial history variables and their estimated correlations with postcardiotomy delirium. Sixteen studies (1, 5, 10, 15–26, 36) assessed the effect of age on postcardiotomy delirium. Only a slight positive correlation was estimated to exist between age and postcardiotomy delirium. These studies, however, generally had a restricted range of ages from which to show an effect. Thus, although the correlation is quite small, it does not necessarily reflect the true relationship between age and postcardiotomy delirium. In fact, if data from studies that used children as subjects were included in these calculations, it is likely that a strong relationship between age and postcardiotomy delirium would be found, since children are reported to be less prone to delirium following open-heart surgery (10, 27).

Sveinsson (26) found a relationship between emotional instability and delirium, while Egerton and Kay (27) found that "marital instability" and "over-

TABLE 1. Estimated Correlations Between Demographic and Psychosocial History Variables and Postcardiotomy Delirium

Variable	Studies That Addressed Variable	Studies That Found an Effect	Subjects		Estimated Correlation (r)
			Mean	Range	
Age	16	12	90	26-204	0.07
Sex	11	2	60	30-182	0.00
Previous psychiatric illness	5	1	75	26-164	0.00
Intelligence	3	1	85	52-164	0.00
Education	2	0	72	60-85	0.00
Family history of psychiatric illness	2	1	41	26-60	0.00

TABLE 2. Estimated Correlations Between Illness Variables and Postcardiotomy Delirium

Variable	Studies That Addressed Variable	Studies That Found an Effect	Subjects		Estimated Correlation (r)
			Mean	Range	
Rheumatic heart disease	3	1	91	79-100	0.00
Noncongenital heart disease	2	2	123	84-164	0.38
History of cerebrovascular disease	2	0	130	100-164	0.00
Significant additional medical problems	2	0	59	26-107	0.00

whelming personal problems" correlate with postcardiotomy delirium. Kornfeld et al. (28) found that the "dominance" score on the 16-Personality Factor Questionnaire was related to postcardiotomy delirium. Finally, Danilowicz and Gabriel (37) found non-English-speakers more likely to manifest postcardiotomy delirium. We did not estimate correlations for these variables, since they were examined in only single studies. No other psychosocial variables, including a history of psychiatric illness, were estimated to correlate with postcardiotomy delirium.

Illness Variables

Table 2 lists illness variables and their estimated correlations with postcardiotomy delirium. Blachly and Starr (15) and Heller et al. (10) found a higher prevalence of delirium in patients with noncongenital heart disease than in patients with congenital heart disease. In these studies, patients with congenital heart disease were younger and less ill before surgery than most of the other patients. Although there was a substantial estimated correlation, the information provided by this correlation is limited because it is confounded by several factors, such as age, degree of illness, and length of time on bypass; the latter factor is significantly shorter in patients with congenital heart disease (10).

Three research groups (17, 26, 30) examined differences in the frequency of delirium in patients receiving surgery because of rheumatic heart disease or because of other diseases. Only one research group (30) found a higher prevalence of delirium in the rheumatic heart disease patients. The other researchers (17, 26) found no difference in the occurrence of postcardiotomy delirium between the groups. Consequently, the estimated correlation between rheumatic heart disease and postcardiotomy delirium is zero.

Nussmeier et al. (20) observed that patients with calcified mitral or aortic valves were significantly more

likely to exhibit neuropsychiatric abnormalities than patients without calcified valves. They attributed the greater frequency of neuropsychiatric complications in the former patients to an increased occurrence of emboli in this group. However, patients with calcified valves typically were older and had longer times or bypass than patients without calcified valves.

Surprisingly, significant additional medical problems, such as concurrent systemic arterial hypertension, were not found to correlate with postcardiotomy delirium by two research groups (21, 24). Nevertheless, Kornfeld et al. (18) found that a history of myocardial infarction significantly correlated with delirium. Estimates of correlations between delirium and calcified valves or history of myocardial infarction were not made because these variables were, again addressed by single studies.

Preoperative Variables

Table 3 lists preoperative variables and their estimated correlations with postcardiotomy delirium. Seven studies (10, 15, 17, 18, 26, 28, 38) addressed the effect of severity of illness, using the New York Heart Association functional class or equivalent. An estimated correlation was found between severity of illness and postcardiotomy delirium. Although the correlation is small, the effect was found in six of the seven studies.

The presence of brain damage, organicity, or abnormal neurological signs before surgery was found to correlate with postcardiotomy delirium. However, this was not found uniformly in all of the five studies (10, 19, 27, 29, 38) that examined these factors. Heller et al. (10) found no effect; thus, the magnitude of the correlation between these factors and postcardiotomy delirium was diminished.

Three studies (19, 25, 44) found that preoperative psychiatric intervention was associated with a low

TABLE 3. Estimated Correlations Between Preoperative, Intraoperative, and Postoperative Variables and Postcardiotomy Delirium

Variable	Studies That Addressed Variable	Studies That Found an Effect	Subjects		Estimated Correlation (r)
			Mean	Range	
Preoperative					
Severity of illness	7	6	108	79-164	0.11
Brain damage/organicity/abnormal neurological signs	5	4	72	58-89	0.10
Psychiatric intervention	3	3	42	20-58	-0.60
Anxiety	3	1	53	58-88	0.00
MMPI/ego strength	2	1	40	30-52	0.00
Psychopathology score/mental status	2	1	49	23-85	0.00
Intraoperative					
Length of time on bypass	12	6	91	30-182	0.00
Complexity of procedure	3	2	84	36-164	0.05
Perfusion flow rate/pressure	3	0	196	182-204	0.00
Hypothermia	3	0	82	79-89	0.00
Length of time anesthesia was administered	3	1	65	26-107	0.00
Mean blood pressure	2	1	151	107-204	0.00
Presence of air/particulate matter emboli	2	1	121	60-204	0.00
Postoperative					
Severity of illness in recovery room	6	5	98	82-142	0.09
EEG abnormality/organicity	4	4	116	76-164	0.40
Sleep deprivation	4	3	83	27-142	0.08
Low cardiac output	3	2	53	34-77	0.06
Time in intensive care unit/recovery room	2	0	68	50-89	0.00

prevalence of delirium. These interviews involved listening to the patient's fears, explaining the procedures, and cautioning the patient not to panic if postoperative confusion occurred. Although a negative correlation between psychiatric intervention and postcardiotomy delirium does not uncover a potential causal agent for the postoperative disorder, it is included here because it has implications for prevention, and indeed was the single most predictive variable for postcardiotomy delirium in this meta-analysis.

Four other preoperative variables were found to correlate with postcardiotomy delirium in single studies. Treatment with thiopental (20) was found to be negatively correlated, while exposure to psychoactive drugs in general (24) was found to be positively correlated with symptoms of delirium. Naber and Bullinger (39) found level of subjective stress and a self-controlling coping style to be associated with postcardiotomy delirium.

Neither anxiety nor ego strength was estimated to be associated with postcardiotomy delirium, due to contradictory findings (1, 5, 18, 19). One study (39) found preoperative score on a psychopathological inventory to be related to delirium, while another (42) found no relationship between preoperative mental status and postcardiotomy delirium. The combination of these results yielded no estimated correlation for this variable.

Intraoperative Variables

Table 3 also lists nine intraoperative variables and their estimated correlations with postcardiotomy delirium. Among these, time on cardiopulmonary bypass was addressed in 12 studies (5, 10, 17, 18, 20-22, 26, 28, 30, 36, 40). Six studies found an effect for this variable; five found no effect, and one study (30) found

a negative correlation between time on bypass and postcardiotomy delirium. Consequently, no overall estimated correlation was found. The complexity/severity of the surgical procedure was found to correlate with postcardiotomy delirium by two (31, 38) of the three (4, 31, 38) studies that examined this factor. None of the other intraoperative variables addressed in replicated studies was estimated to correlate with postcardiotomy delirium.

A number of unreplicated studies reported correlations between additional intraoperative variables and postcardiotomy delirium. The use of a disk oxygenator (10), lowest arterial pressure during time on bypass (22), and surgical complications (i.e., increases in anesthesia hours, pump time, units of blood, and hypothermia) (15) were estimated to correlate with postcardiotomy delirium.

Postoperative Variables

Table 3 also lists postoperative variables and their estimated correlations with postcardiotomy delirium. Global severity of illness in the recovery room, which was addressed in six studies (10, 18, 26, 28, 38, 41), was correlated with postcardiotomy delirium. This variable, however, involves such a large cluster of factors that it does not illuminate a discrete area of risk. Sensory monotony, sleep deprivation, hypotension, and hypoxia are just some of the many variables subsumed by this broad variable. One of these variables, sleep deprivation, was specifically examined in four studies (10, 18, 28, 42). A modest correlation was estimated to exist for this variable. In an attempt to determine whether sleep loss actually precedes delirium, Harrell and Othmer (43) found that although sleep loss was correlated with postcardiotomy delirium, the

insomnia *followed* rather than preceded it. Postoperative EEG abnormality or organicity, examined by four studies (15, 38, 41, 42), was uniformly found to correlate with delirium.

Blachly and Kloster (31) and Heller et al. (32) found cardiac output to be related to postcardiotomy delirium. Blachly and Kloster (31) found that patients who showed a low cardiac output during the first several postoperative days often experienced hallucinations. The onset of these symptoms generally paralleled a rapid rise in cardiac output from lower levels. Heller et al. (32) also observed an association between postcardiotomy delirium and low cardiac output. On the other hand, McClish et al. (40) failed to find an association between low cardiac output and postcardiotomy delirium. These combined results form the estimated correlation in table 3.

Serum level of anticholinergic drugs (33) and tracheostomy (34) were addressed in single studies and were found to correlate with postcardiotomy delirium.

Single Studies

As mentioned earlier, a number of predictor variables were addressed by single studies only. Applying meta-analytic techniques to the findings of single studies is, technically, a contradiction. A number of variables were found to be unrelated to postcardiotomy delirium in unreplicated studies. They were emotional instability, marital instability, marital status, occupation, overwhelming personal problems, work performance, race, social class, exposure to psychoactive drugs, disk oxygenator, duration of low perfusion pressure, duration of procedure, surgical complications, body temperature on first postoperative day, hypokalemia, hypoxemia, pneumonitis, and tracheostomy. However, there were significant associations ($p < 0.05$) between the following variables addressed in unreplicated studies and postcardiotomy delirium: dominance ($N=142$ subjects), non-English-speaking ($N=102$), calcified mitral or aortic valves ($N=182$), history of myocardial infarction ($N=88$), no pretreatment with thiopental ($N=182$), subjective stress level preoperatively and postoperatively ($N=23$), self-control coping style ($N=23$), lowest arterial pressure during bypass ($N=50$), and serum level of anticholinergic drugs postoperatively.

COMMENT

Any time one summarizes findings from a number of studies, there are risks of distortion because of important differences across the studies. Before discussing our major observations, we wanted to acknowledge the potential drawbacks of our analyses. To begin with, there is some dispute in the literature about the definition of postcardiotomy delirium. Some investigators (10, 28, 32) favor a diagnosis of postcardiotomy delirium when the delirium follows a lucid interval of

2 to 5 days following surgery. There is, however, no consensus in the literature on this distinction. Fewer than half of our studies even mentioned the onset times, let alone provided an analysis of risk factors keyed to specific delirium onset times. Due to the limited replication and insufficient reporting of onset times, we reviewed all studies that reported postcardiotomy delirium regardless of whether the delirium was preceded by a lucid interval. Were the literature more complete, one would be interested in investigating whether the risk factors for an immediate onset of postcardiotomy delirium are different from those associated with a delayed onset of postcardiotomy delirium.

Another criticism of our study might be that we have tried to summarize findings across 25 years despite the fact that medical and surgical techniques have changed dramatically. Curiously, our results have shown that the overall prevalence of postcardiotomy delirium has remained fairly constant at 32% across the two blocks of years, 1963–1974 and 1975–1987. Thus, there seems to be little reason for analyzing the data separately according to time of publication. Nevertheless, in recent years there have been fewer reported cases of deliria that present with hallucinations, paranoid ideation, or agitation and more reported cases of deliria manifested by symptoms such as disorientation to place or time. This apparent shift in the clinical presentation of delirium may be explained by the increased reliance on interviews as opposed to chart reviews for researching this area. In addition, this change in the clinical manifestation of postcardiotomy delirium may reflect the increased number of coronary artery bypass graft procedures being performed in recent years.

One of the functions of meta-analysis is to point out areas that need to be addressed in future studies. We have already mentioned that future studies need to specify the time of onset of delirium as well as to describe the relationship between the risk factors and the specific symptomatic presentation of delirium, as opposed to just the presence or absence of delirium. Reliance on personal observation and interviews, as opposed to chart reviews, promises to provide more detailed and comprehensive data on postcardiotomy delirium. Moreover, *all* patients in a study should be observed and interviewed. This will ensure that inconspicuous manifestations of delirium will not go unnoticed. An additional desirable aim of future studies would be to provide more of the raw data about the relationship between risk factors and postcardiotomy delirium, rather than just a p value. Since such data were reported sparsely, we were obliged to employ the vote-count method of meta-analysis, which provides a less precise estimate of the relationship between risk factors and postcardiotomy delirium, given the number of studies we have examined. As a result, the estimated correlations reported in tables 1–3 have wide confidence intervals. Finally, it is disappointing that such a large number of variables have been studied,

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with so few efforts at replication. Well-designed studies of previously investigated variables are needed and will add to our understanding and confidence in the findings.

This review should serve as a first pass at trying to analyze this complex and important area. With these caveats in mind, we will review the most striking findings.

The studies suggest that roughly one-third of all cardiomy patients experience a postoperative delirium, a not insubstantial number given that 170,000 patients per year undergo coronary artery bypass grafts in the United States alone (53). We find no evidence to support the clinical impression that postcardiotomy delirium has declined. It may be that we are now so prepared for this eventuality that it is less dramatic to today's health care provider, who routinely tries to limit postcardiotomy delirium through preoperative teaching, continuing postoperative orientation, psychiatric consultation, and/or psychopharmacologic intervention. The potential benefit of preoperative psychiatric consultation to help lessen the prevalence of delirium is evidenced by the combined findings that formed the largest estimated correlation in this review. Given the percentage of individuals who become delirious following open-heart surgery, further controlled studies of the preventive value of preoperative psychiatric interventions are in order.

In any event, the high prevalence of postcardiotomy delirium and the fact that the prevalence is unchanged despite 25 years of ever more polished surgical and medical techniques suggest that we are not particularly close to understanding its etiology.

The studies we have reviewed do not pinpoint any precise risk factor *consistently*. For instance, although historically, medical personnel have suggested that sleep deprivation and immobilization on the intensive care unit may be, in part, responsible for postcardiotomy delirium, we did not find a relationship between time on the intensive care unit and postcardiotomy delirium, and we found only a slight relationship between sleep deprivation and postcardiotomy delirium. Similarly, even bypass time did not hold up as a robust predictor of postcardiotomy delirium when the data from 12 studies were considered. There are a number of tantalizing observations made by single studies; however, unfortunately, many of these observations have never been replicated. Where there was replication, one is struck by the relatively low order of magnitude of the estimated correlation with postcardiotomy delirium; the estimated correlation exceeded 0.30 for only two of the risk factors (not including absence of preoperative psychiatric intervention)—postoperative EEG abnormality and noncongenital heart disease.

This would appear to be an instance when clinical intuition is misleading. Postcardiotomy delirium is as prevalent as ever, and the risk factors are not understood. Given the large number of patients who are at risk for postcardiotomy delirium, further study is indicated.

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The Diagnostic Implications of Formal Thought Disorder in Mania and Schizophrenia: A Reassessment

V. Chowdary Jampala, M.B., B.S., Michael Alan Taylor, M.D., and Richard Abrams, M.D.

The authors compared nine manic patients exhibiting formal thought disorders (tangentiality, neologisms, drivelling, private use of words, and paraphasias) with 102 manic patients without these thought disorders and with 31 schizophrenic patients. Manic patients with formal thought disorders tended to have more "schizophrenic" symptoms than did manic patients without formal thought disorders, but both groups improved significantly more during the index episode than did the schizophrenic patients. Although the prevalence of flight of ideas was high in mania, narrowly defined formal thought disorder was rare, suggesting that precise definition and description of thought disorders would be helpful in distinguishing mania from schizophrenia.

(Am J Psychiatry 1989; 146:459-463)

Thought disorder in psychiatric patients has been systematically studied by several investigators (1-18). Although the term "thought disorder" usually refers to disturbances of speech rather than of thought processes (12), investigators (4, 15) have argued for continued use of the term because the language disturbances in psychiatric patients are different from those usually observed in patients with pure aphasia and, therefore, must reflect underlying disturbances in thinking processes. There is no agreement among researchers and practitioners on the definition of phenomena traditionally included under the rubric of

thought disorder. Some writers (5, 9, 14) have been more specific in their definitions and descriptions, stressing specific disturbances in the form rather than in the content of speech and using the term "formal thought disorder" to reflect these disturbances. Two of us (R.A. and M.A.T.) (19) characterized formal thought disorder as nonsequitive speech, tangential speech, drivelling, neologisms, paraphasias, and private use of words. We did not include flight of ideas, a characteristic speech pattern of mania. On the other hand, one of the formal thought disorders included—nonsequitive speech (i.e., giving answers that do not follow the questions asked)—might be a form of flight of ideas, having its origin in the racing thoughts and distractibility often seen in manic patients.

For some time, formal thought disorder was considered a core feature of schizophrenia. More recently, however, several investigators (1-11, 13-18) have reported that thought disorder is not specific to schizophrenia and may occur in several other conditions, most notably mania. Some of these reports (11, 13, 15) concluded that thought disorder occurs with equal severity in schizophrenic and manic patients, but others (8, 11, 14, 18) have commented on the differing forms of the thought disorder that occur in these states, and still others (19, 20) have stated that the presence of thought disorder in manic patients does not predict their clinical characteristics, family history, or response to treatment. Thus, the diagnostic, prognostic, and pathogenic implications of thought disorder in psychiatric patients, particularly manic and schizophrenic patients, remain unclear, and the resolution of these issues obviously depends on how these phenomena are defined.

In the light of the confusion surrounding the clinical and theoretical implications of formal thought disorder, we reexamined our original data (19) to assess the predictive value of narrowly defined formal thought

Received Feb. 10, 1988; revision received Aug. 30, 1988; accepted Sept. 30, 1988. From the Department of Psychiatry and Behavioral Sciences, University of Health Sciences/The Chicago Medical School, and the VA Medical Center, North Chicago. Address reprint requests to Dr. Jampala, Department of Psychiatry and Behavioral Sciences, University of Health Sciences/The Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064.

disorder in manic and schizophrenic patients for outcome and other variables.

METHOD

The original study was done on an acute-treatment university psychiatric inpatient unit of a public hospital serving a suburban-rural catchment area in New York State. It included all patients consecutively admitted during a 22-month period ending in May 1976. Data collection and diagnostic methods have been described in detail previously (19). A semistructured interview was used to collect the necessary clinical and demographic data from each patient. Thought disorders, as defined in appendix 1, were assessed during the index episode. Severity of illness on admission and again at discharge was assessed by using a scale with half-step increments ranging from 0 (not ill) to 4 (most severely ill). A complete family history (relatives diagnosed blindly and independently from probands) was obtained from each proband and at least one first-degree relative, if available. An EEG was routinely obtained in all cooperative patients while awake and while asleep and was interpreted without awareness of proband diagnosis. For the present study, the diagnosis of mania was made by using Washington University criteria (21) and the diagnosis of schizophrenia was made by using Taylor-Abrams criteria (22).

Among-group differences for continuous variables were tested by using one-way analyses of variance and Scheffé's post hoc test for multiple comparisons; categorical variables were compared by using chi-square.

RESULTS

Of 465 patients admitted during the study period, 111 satisfied the Washington University criteria for mania and 31 satisfied the Taylor-Abrams criteria for schizophrenia. When defined narrowly (i.e., excluding nonsequitive speech), the formal thought disorders characteristic of schizophrenia were present in only nine (8.1%) of the manic patients, compared with 14 (45.2%) of the 31 schizophrenic patients (table 1). Only one (0.9%) of the manic patients had two of the narrowly defined formal thought disorders listed in table 1, compared with six (19.4%) of the schizophrenic patients. If nonsequitive speech is included to expand the definition of formal thought disorder, 20.7% of the manic patients exhibited formal thought disorder, compared with 51.6% of the schizophrenic patients. If flight of ideas is also defined as a formal thought disorder, 74.8% of the manic patients had formal thought disorder, compared with 51.6% of the schizophrenic patients. Of the 16 manic patients who exhibited nonsequitive speech, 15 also exhibited flight of ideas and only two exhibited other formal thought disorders.

Nine (8.1%) of the 111 manic patients exhibited

TABLE 1. Thought Disorders in Inpatients With Mania or Schizophrenia

Thought Disorder	Schizophrenia (N=31)		Mania (N=111)	
	N	%	N	%
1. Flight of ideas	3	9.7	80	72.1
2. Nonsequiturs	11	35.5	16	14.4
3. Tangentiality	6	19.4	1	0.9
4. Drivelling	5	16.1	1	0.9
5. Neologisms	5	16.1	3	2.7
6. Private use of words	4	12.9	2	1.8
7. Paraphasias	3	9.7	3	2.7
8. Any one of 3-7	14	45.2	9	8.1
9. Any one of 2-7	16	51.6	23	20.7
10. Any one of 1-7	16	51.6	83	74.8
11. Any two of 3-7	6	19.4	1	0.9
12. Any two of 2-7	10	32.3	3	2.7
13. Any two of 1-7	11	35.5	21	18.9

formal thought disorders other than flight of ideas or nonsequitive speech. These nine manic patients were compared with the 102 manic patients without formal thought disorder and with the schizophrenic patients.

Tables 2 and 3 compare the course of illness and other clinical features of the three diagnostic groups. Manic patients with formal thought disorder exhibited a trend for an earlier age at onset of illness than manic patients without formal thought disorder (table 2). Significantly more of the manic patients with formal thought disorder than of manic patients without formal thought disorder exhibited lability of mood and denudative behaviors (table 3). Manic patients with formal thought disorder exhibited a trend for higher catatonia scores, a composite variable representing the sum of all catatonic symptoms. Their mean catatonia score was 0.9 ± 1.7 , compared with 0.3 ± 0.8 for manic patients without formal thought disorder ($t=1.95$, $df=109$, $p=0.054$). Manic patients with formal thought disorder also showed a trend for higher schizophrenia scores, a composite variable representing the sum of symptoms often associated with schizophrenia (delusions of persecution, any catatonic symptom, auditory hallucinations, and first-rank symptoms) (table 2). The manic patients with formal thought disorders also exhibited a trend for higher lifetime exposure to neuroleptics (table 2). During the index admission, however, both groups of manic patients received similar treatments and exhibited the same degree of improvement.

Manic patients with formal thought disorder differed from schizophrenic patients (apart from the increased prevalence of manic symptoms, a selection artifact) only in that more of the manic patients were rated as more severely ill than were the schizophrenic patients at the time of admission and as less severely ill at discharge; they also exhibited a higher percentage of improvement (table 2).

Schizophrenic patients exhibited a trend for an earlier onset of illness than manic patients without formal thought disorder (table 2) and had a higher prevalence of motor retardation, auditory hallucinations, first-

TABLE 2. Course of Illness and Clinical Features of Inpatients With Schizophrenia, Mania With Formal Thought Disorder, or Mania Without Formal Thought Disorder

Item	Schizophrenia (N=31)		Mania With Thought Disorders (N=9)		Mania Without Thought Disorders (N=102)		F (df=2, 139)	p ^a
	Mean	SD	Mean	SD	Mean	SD		
Age at index admission (years)	37.9	11.2	37.1	11.7	40.6	12.5	0.82	0.44
Age at onset (years)	25.3	7.3	25.0	9.1	29.7	10.7	2.98	<0.054
Number of hospitalizations	4.5	3.7	5.8	2.9	5.1	3.8	0.52	0.60
Lifetime exposure to neuroleptics (months)	33.9	50.2	25.4	30.3	13.3	26.5	4.76	<0.01 ^b
Duration of index admission (days)	54.9	38.3	48.9	28.7	42.1	39.4	1.33	0.27
Duration of present illness (months)	4.0	4.6	1.4	1.8	0.9	1.0	20.79	<0.0001 ^{b, c}
Illness ratings								
Severity at admission ^d	2.9	0.4	3.5	0.5	3.3	0.5	7.82	<0.0006 ^{b, c}
Severity at discharge ^d	1.9	1.0	0.6	0.8	0.5	0.8	33.27	<0.0001 ^{b, c}
Percent of improvement	34.5	33.0	83.3	24.0	83.4	25.3	39.57	<0.001 ^{b, c}
Composite schizophrenia score ^e	1.5	1.1	1.2	1.1	0.6	0.8	12.23	<0.0001 ^{b, f}

^aBonferroni-corrected significance at $p < 0.005$.

^bDifference between manic patients without formal thought disorder and schizophrenic patients significant at $p < 0.05$, Scheffé's post hoc test.

^cDifference between manic patients with formal thought disorder and schizophrenic patients significant at $p < 0.05$, Scheffé's post hoc test.

^dRated on a scale with half-step increments on which 0=not ill and 4=most severely ill.

^eSum of ratings for delusions of persecution, any catatonic symptom, auditory hallucinations, and first-rank symptoms.

^fDifference between manic patients with and without formal thought disorder significant at $p < 0.06$, Scheffé's post hoc test.

TABLE 3. Selected Clinical Features of Inpatients With Schizophrenia, Mania With Formal Thought Disorder, or Mania Without Formal Thought Disorder

Clinical Feature	Schizophrenia (N=31)		Mania With Thought Disorders (N=9)		Mania Without Thought Disorders (N=102)		χ^2 (df=2)	p ^a
	N	%	N	%	N	%		
Lability of mood	3	9.7	5	55.6	54	52.9	18.64	<0.001 ^b
Denudative behaviors	0	0.0	3	33.3	5	4.9	14.94	<0.001 ^c
Motor retardation	6	19.4	0	0.0	3	2.9	11.44	<0.005 ^d
Any catatonic symptom	12	38.7	3	33.3	16	15.7	8.10	<0.02 ^e
Delusions of persecution	15	48.4	5	55.6	32	31.4	4.45	0.11
Auditory hallucinations	17	54.8	3	33.3	19	18.6	15.82	<0.001 ^d
First-rank symptoms	16	51.6	3	33.3	14	13.7	19.68	<0.001 ^d

^aBonferroni-corrected significance at $p < 0.003$.

^bDifference between manic patients without formal thought disorder and schizophrenic patients significant at $p < 0.001$; difference between manic patients with formal thought disorder and schizophrenic patients significant at $p < 0.002$, chi-square post hoc test.

^cDifference between manic patients with formal thought disorder and schizophrenic patients significant at $p < 0.001$; difference between manic patients with and without formal thought disorder significant at $p < 0.002$, chi-square post hoc test.

^dDifference between manic patients without formal thought disorder and schizophrenic patients significant at $p < 0.001$, chi-square post hoc test.

^eDifference between manic patients without formal thought disorder and schizophrenic patients significant at $p < 0.006$, chi-square post hoc test.

rank symptoms, and catatonic symptoms (table 3). More (N=13, or 48.1%) of the 27 schizophrenic patients for whom data were available than of the 84 manic patients for whom data were available (N=22, or 26.2%) exhibited EEG abnormalities. Like manic patients with formal thought disorder, manic patients without formal thought disorder were rated more severely ill than schizophrenic patients at admission and less severely ill (and more improved) than schizophrenic patients at discharge (table 2).

Examination of the prevalence of psychiatric illness among the first-degree relatives revealed a trend for more manic patients with formal thought dis-

order (N=5, or 55.6%) to have a first-degree relative suffering from affective illness than manic patients without thought disorders (N=27, or 27% of the 100 patients with an available family history) or schizophrenic patients (N=6, or 20% of the 30 patients with an available family history) ($\chi^2=4.43$, $df=2$, $p=0.11$).

DISCUSSION

Research (11, 13, 15) suggests that thought disorders are as frequent and as severe in mania as they are in schizophrenia. However, as noted by some investi-

gators (8, 11, 14, 18), the thought disorders observed in mania are qualitatively different from those observed in schizophrenia. Our results support the latter view and suggest that the characteristic thought disorders of schizophrenia occur infrequently in mania, even though the overall disturbance in speech (in the form of flight of ideas) might be more frequent.

The number of manic patients with narrowly defined formal thought disorder in our sample was quite small, and a comparison of this group with others risks missing true between-group differences because of small sample size. However, any differences found to be significant are likely to be robust. In our sample, manic patients with formal thought disorder exhibited a higher prevalence of some manic symptoms as well as a trend for higher prevalence of catatonia, first-rank symptoms, and auditory hallucinations than manic patients without formal thought disorder, although both groups, unlike the schizophrenic patients, responded well to treatment. These findings suggest that manic patients with formal thought disorder may have a more severe rather than a different condition than manic patients without formal thought disorder. The fact that more manic patients with formal thought disorder had a first-degree relative with affective illness supports this interpretation. The presence of formal thought disorder might serve as a severity index in manic patients. Since we do not have adequate information regarding the cross-sectional presentations of these patients during their other illness episodes or about the course of their illnesses, we cannot draw any conclusions about the recurrence of formal thought disorder or the usefulness of formal thought disorder as an indicator of subsequent course in patients with mania.

No category of thought disorders was unique to any diagnostic group: 8.1% of manic patients had thought disorders usually associated with schizophrenia, and 9.7% of schizophrenic patients exhibited flight of ideas, a thought disorder usually associated with mania. This overlap suggests that it is fallacious to think that the presence of any one thought disorder is diagnostic of a particular psychiatric illness. It does not, however, mean that thought disorders have no diagnostic value. In our sample, if a patient had one of the formal thought disorders of tangentiality, drivelling, neologisms, private use of words, or paraphasias, the odds of that person receiving a research diagnosis of schizophrenia were almost one in two, compared with one in 12 for the diagnosis of mania. Only one (0.9%) of 111 manic patients exhibited two of these thought disorders, compared with six (19.4%) of 31 schizophrenic patients. With regard to diagnostic sensitivity, the presence of one of these thought disorders as diagnostic of schizophrenia would provide an odds ratio of 8.4 compared with 26.4 when two or more of the formal thought disorders are used as indicating the presence of schizophrenia, a three-fold increase. This sensitivity can probably be increased further when other criteria are also taken into account.

DSM-III-R gives less weight to thought disorders than to other symptoms for the diagnosis of schizophrenia. The presence of incoherence or loosening of associations alone does not meet *DSM-III-R* criteria for a diagnosis of schizophrenia. Either delusions, hallucinations, catatonic behavior, or flat or grossly inappropriate affect must also be present. In addition, *DSM-III-R*'s descriptions of thought disorders are rather vague and nonspecific. We suggest that the sensitivity and validity of *DSM-III-R* criteria for the diagnosis of schizophrenia could be enhanced by providing detailed descriptions of specific formal thought disorders and by modifying the schizophrenia criterion A(1) so that the presence of two or more of these thought disorders alone would satisfy that criterion.

Although the manic patients with formal thought disorder in our study had more associated symptoms than the manic patients without formal thought disorder, both groups of manic patients received similar treatment and improved significantly more than the schizophrenic patients during the index admission. This suggests that despite being more severely ill, manic patients with formal thought disorder are as treatment responsive as manic patients without formal thought disorder and that the presence of thought disorders does not appear to have any prognostic value in mania. These results are consistent with earlier research addressing the presence of schizophrenic symptoms in mania (19, 20, 23, 24), which has consistently demonstrated that thought disorders, catatonic symptoms, hallucinations, and delusions of persecution are useful only as indexes of severity and not as discriminants of manic from schizoaffective patients. Except in the presence of emotional blunting (25), patients with manic symptoms generally appear to have better treatment responses and prognoses regardless of the presence of other symptoms.

In summary, we suggest that narrowly defined formal thought disorder is uncommon in mania and when present may indicate a severe but treatment-responsive subtype of manic illness. No particular type of thought disorder can be construed as diagnostic of either mania or schizophrenia, although the presence of two or more narrowly defined formal thought disorders is highly suggestive of schizophrenia. The presence of thought disorder in mania appears to have little prognostic value.

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APPENDIX 1. Formal Thought Disorders

Tangential speech: tightly linked associations that go off on a tangent and bypass the goal; giving answers that are around but not to the point; giving answers that do not explain. For example, the answer to the question, "Where do you live?" might be, "I live alone." The answer to "What is your address?" might be, "You know, a good place to live is hard to find these days." The answer to "I understand that, but I am interested in knowing where you live," would be "I have been living in the same apartment for the last ten years, but the neighborhood is really going down the drain."

Drivelling speech: utterances in which the syntax appears to be intact but the meaning is lost; double talk. For example, "He had to be the one to do it or find it in itself, besides which, it wasn't the thing he had."

Neologism: an utterance that forms a new word (i.e., a phoneme string) and that may be used idiosyncratically. For example, "They wanted to trixicate me, but I wouldn't let them."

Private use of words: common words or phrases used without any obvious understandable connection to their accepted meaning; similar to semantic (out-of-word-class) paraphasia. For example, "I had to mechanistic them in order to be safe."

Paraphasia: a word or short phrase that has approximate meaning; unlike private use of words, paraphasias are able to convey meaning and have some obvious connection to the accepted, more appropriate utterance. For example, "The wind blew off my head-covering."

Nonsequiturs: in the absence of flight of ideas, utterances that are unconnected in meaning to the preceding question or to the subject's speech. For example, the answer to the question, "When was the last time you saw your children?" might be, "I am a very special person."

Flight of ideas: associations (usually voluminous) that do not get to the point and often include multiple recurrent themes; distractible speech in which the associations are to a variety of external as well as internal stimuli regardless of the logical point to be made. For example, "Well, all I can say is that I was upset. Look at what they did to my car. I bought it in 1979, you know, the year we had that big snow. Something is wrong this year—it is too mild. Perhaps it is the greenhouse effect, or the ozone layer destroyed by the hydrocarbons. But I am not going to let the damn government tell me what I spray around my house, we've had bugs all over the place."

Temporal Lobe Pathology in Schizophrenia: A Quantitative Magnetic Resonance Imaging Study

Richard L. Suddath, M.D., Manuel F. Casanova, M.D., Terry E. Goldberg, Ph.D.,
David G. Daniel, M.D., John R. Kelsoe, Jr., M.D., and Daniel R. Weinberger, M.D.

Although numerous studies have confirmed the presence of larger cerebral ventricles in schizophrenia, the locus of tissue loss remains elusive. By analyzing magnetic resonance scans with computerized image analysis, the authors determined gray and white matter volumes in the temporal lobes and prefrontal regions of 17 patients with schizophrenia and 17 age- and sex-matched normal subjects. The volume of temporal lobe gray matter was 20% smaller in the patients than in the control subjects. The lateral ventricular volume was 67% larger in the patients and, when normalized for brain size, correlated inversely with the volume of temporal lobe gray matter.

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Over the past 10 years there has been renewed interest in neuroanatomical studies of schizophrenia. This interest has been kindled primarily by the observation of large cerebral ventricles on computerized tomography (CT) scans (1). This finding suggests that somewhere in the brain there has been either loss of tissue or a failure of development. More recently, efforts have focused on specific brain regions where this pathology might be located. Several post-mortem studies have reported diencephalic and limbic pathology in schizophrenia (2-4), yet pathology in other sites, such as the frontal cortex (5), and diffuse pathology (6) have also been described. While each of these findings might be associated with large cerebral ventricles, convincing direct in vivo evidence that large ventricles are related to pathology of a particular neuroanatomical structure has not been produced.

Magnetic resonance imaging (MRI) makes it possible to examine living subjects to determine brain pathology that has previously been observed only in post-mortem studies. In comparison with CT, MRI provides finer spa-

tial resolution and a greater ability to discern subtle differences in tissue composition. In an earlier MRI study (7) we determined the volume of the lateral and third ventricles, prefrontal region, temporal lobe, and the amygdala-hippocampal complex in patients with schizophrenia and in normal control subjects. While we confirmed that the patients with schizophrenia had larger lateral and third ventricles, we were unable to demonstrate that the volume of any of the gross regions examined was smaller. Neither did we find a correlation between ventricular size and the volume of any specific brain region. However, the sensitivity of the technique used in our prior study was limited in that it did not permit the distinct measurement of gray and white matter within a region. Also, the measurements were performed manually, which may have reduced sensitivity or introduced subtle unreliability.

In the present study we have further pursued our search for structural pathology with a new method, which combines MRI with a computerized image analysis system. This latter method has several advantages, including contrast enhancement, image magnification, color coding, and automated edge detection. With this technique it is possible to quantify gray and white matter volumes. We report herein a significantly smaller temporal lobe gray matter volume in patients with schizophrenia than in normal subjects. We also offer preliminary evidence that temporal lobe gray matter volume correlates inversely with lateral ventricular volume.

METHOD

Subjects

Twenty-two inpatients from NIMH research wards who fulfilled the *DSM-III* criteria for chronic schizophrenia volunteered and gave informed consent for an MRI procedure. The scans of five patients were excluded from analysis because of excessive movement artifact. Of the remaining 17 subjects, 10 were male and seven were female. Seven of these patients had been included in the earlier study (7). After the patients were admitted to our research units, *DSM-III* diagnoses were made during ongoing clinical evaluations by two or more research psy-

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chiatrists. The diagnoses were determined before we obtained and analyzed the results of the structural neuroimaging (MRI or CT scanning). Thus, the psychiatrists who performed the diagnostic evaluations were blind to the results of the MRI scans. Of the patients volunteering for this study, two (one male, one female) had persistent tardive dyskinesia at the time the scans were obtained. The subtypes of chronic schizophrenia were distributed as follows: undifferentiated, $N=12$; paranoid, $N=3$; disorganized, $N=1$; residual, $N=1$. As a group, these patients experienced chronic thought disorder and/or auditory hallucinations and, generally, had had incomplete responses to neuroleptic treatment. All of the patients had been treated with neuroleptics at some time during their illnesses. None was receiving medications known to affect brain size (e.g., steroids). The patients were also given medical and neurological examinations, and all received routine blood chemistry tests, VDRL, thyroid function tests, chest X-rays, ECGs, and EEGs.

Seventeen age- and sex-matched subjects, recruited either from hospital personnel or from the community, gave informed consent for an MRI procedure. Ten of the normal control subjects had been included in the earlier study (7). None had a history of serious medical, neurological, or psychiatric illness. None was taking medications known to affect brain size. There were no significant differences between the patient and control groups in age ($\text{mean} \pm \text{SD} = 30.6 \pm 6.5$ and 33.2 ± 7.0 years, respectively) or height (171.9 ± 11.7 and 173.7 ± 9.9 cm).

MRI Scans

All subjects were scanned on a Picker superconducting magnetic resonance imaging system with a 0.5-tesla magnet. The scanning sequence consisted of a midsagittal pilot scan followed by an inversion recovery sequence: inversion time (TI), 600 msec; echo time (TE), 30 msec. Each subject's head was oriented in the scanner by laser to the canthomeatal plane. We obtained scans of 12 contiguous coronal sections, each of which was 1 cm thick, began at the leading edge of the frontal pole, and extended to within 1 to 2 cm of the occiput. For four of the subjects (two male patients, two male control subjects) the full sequence was not completed because of technical error, allowing only frontal lobe measurements to be obtained. All scans were read by radiologists at the National Institutes of Health and were said to show no gross pathological lesions.

Anatomical Measurements

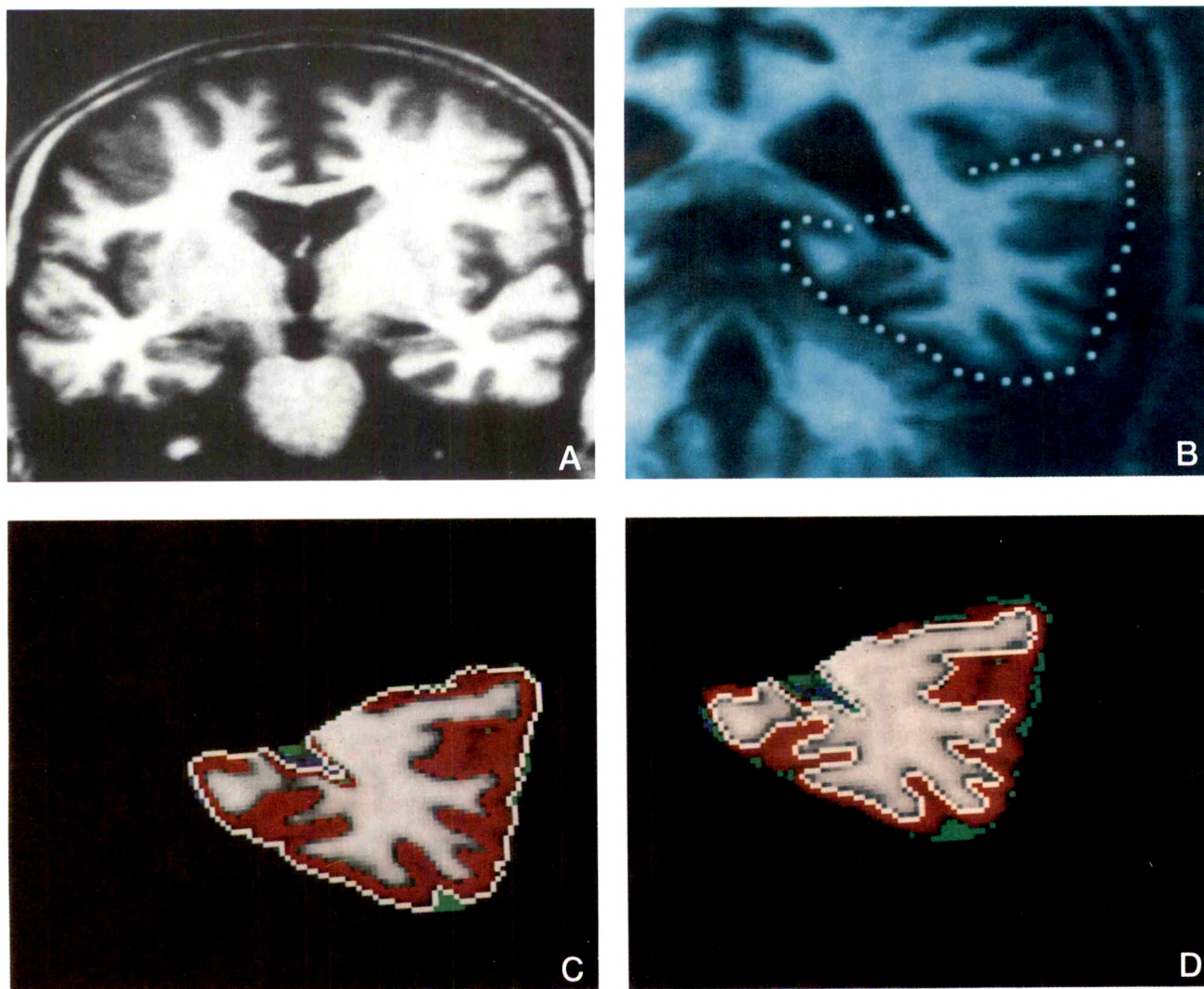
Neuroanatomical structures were identified with the assistance of brain and MRI atlases (8, 9). The prefrontal region was defined as all sections (3 or 4 slices) anterior to the genu of the corpus callosum. The temporal lobe sections (6–8 slices) began with the anterior pole and extended posteriorly to the last section in

which the Sylvian fissure was visualized, usually 1 cm posterior to the pulvinar. In the anterior sections the temporal pole was readily defined by its own anatomical boundaries. The temporal lobe boundary in each central section was defined by drawing a line joining the inferior-most aspect of the Sylvian fissure to the temporal horn of the lateral ventricle. To define the most posterior temporal lobe section, a line was drawn joining the medial-most aspect of the Sylvian fissure to the lateral ventricle. These lines were drawn perpendicular to the axis of the temporal stem (see figure 1). The lateral cerebral ventricles were measured in each section in which they appeared. Each structure was measured bilaterally. The areas of gray and white matter and of the lateral cerebral ventricles in each section were measured by means of a computerized image analysis system. These areas were then summed to produce estimates of the volumes of these structures.

A Loats computerized image analysis system (10) was used to quantify the regions of interest. This system consists of a light box, a video camera, and an image processor (digitizer) within the computer. Before the MRI measurements were made, a standardized series of adjustments was made on the system. The input light intensity was maximized and standardized. Corrections were performed for unevenness in the background illumination. The camera height was set at 64 cm, resulting in an image magnification of $2.8\times$ and a resolution of 0.31 mm. MRI films (hard copies) were then placed over the light box and digitized 16 times, and the average optical density per pixel was calculated. Measurements for each patient were calibrated with the scale determined for each MRI film at the time of the scan. This process corrected for variations in magnification between scans. Since the MRI internal standard reflects in vivo distance, the measurements obtained approximate actual volumes.

A "boundary function" was used to isolate the particular brain region under study. An automated edge detection technique was then employed to delineate the perimeter of the region of interest and compute its area in square centimeters (see figure 1). In the posterior sections of the temporal lobe, a "polygon function" was used to outline the region of interest. Differentiation of gray matter, white matter, and CSF was facilitated by the 64-color color coding function. The color divisions chosen to represent the boundaries between gray matter, white matter, and CSF were the ones that most closely approximated the divisions visualized on the MRI inversion recovery sequence and in anatomical atlases (8, 9). The coding scheme was initially standardized and then uniformly applied to the measurement of all scans.

The structural measurements were performed by two independent raters who were blind to the identity of the subjects. Each brain region was measured three times by the rater, and the mean of the three measurements was used. Interrater reliability was ascertained by having each rater independently measure the same three scans, which required a total of 48 different co-

FIGURE 1. Computer-Assisted Boundary Function for Defining Temporal Lobe Areas on Magnetic Resonance Scans^a

^aA: unenhanced MRI inversion recovery (TI, 600 msec; TE, 30 msec) coronal image at the level of the middle temporal lobe in a patient with schizophrenia. B: enhanced and magnified coronal MRI image at a level 1 cm posterior to the pulvinar, illustrating use of the computer-assisted boundary function to define the posterior temporal lobe by drawing a line perpendicular to the temporal stem and connecting the Sylvian fissure and the lateral ventricle. C: same level as B, illustrating the applied boundary function, enhancement, color coding, and automated edge detection to define the outer border of the temporal lobe gray matter. D: same level as C, illustrating definition of the temporal lobe white matter.

measurements for the prefrontal region and a total of 52 different comeasurements for the temporal lobe. The intraclass correlations were 0.98 for the prefrontal region measurements and 0.92 for the temporal lobe measurements. As a further test of interrater reliability, rater was included as a factor in a multivariate analysis of variance (MANOVA) and failed to reach significance as a main effect (temporal lobe: $F=0.48$, $df=4, 24$, Wilks lambda=0.92, $p=0.75$; prefrontal lobe: $F=0.16$, $df=4, 24$, Wilks lambda=0.97, $p=0.95$) or in interaction with diagnosis (prefrontal lobe: $F=1.45$, $df=4, 24$, Wilks lambda=0.81, $p=0.25$; temporal lobe: $F=0.39$, $df=4, 24$, Wilks lambda=0.93, $p=0.81$).

Data Analysis

The areas of the regions of interest were totaled to generate estimates of the volumes of the following: prefrontal gray and white matter, temporal lobe gray matter (including cortex and subcortical structures), temporal white matter, and lateral ventricles. Temporal lobe gray matter was further subdivided into anterior (first section), central (middle section; when an even number of slices occurred, the more anterior middle slice was chosen), and posterior regions (last section) to more precisely localize the volume differences.

These calculated volumes were treated as dependent variables in a MANOVA performed according to the

TABLE 1. Temporal Lobe Volumes of 15 Schizophrenic Patients and 15 Age- and Sex-Matched Normal Control Subjects

Measure	Volume (cm ³)				t ^a	p
	Control Subjects		Schizophrenic Patients			
	Mean	SD	Mean	SD		
Total gray matter						
Right	50.2	9.6	41.2	9.4	2.59	0.02
Left	46.3	10.3	36.6	11.7	2.42	0.02
Right plus left	96.5	19.1	77.8	19.8	2.64	0.01
Total white matter						
Right	35.4	8.9	31.5	7.9	1.29	0.21
Left	27.8	9.0	28.1	7.6	0.10	0.92
Total temporal lobe						
Right	85.6	14.4	72.7	15.3	2.39	0.02
Left	74.1	15.6	64.6	18.0	1.53	0.13
Right plus left	159.7	28.6	137.3	32.5	2.00	0.05
Anterior gray matter ^b						
Right	3.1	1.3	2.5	1.2	1.25	0.22
Left	2.8	1.4	2.1	1.2	1.40	0.18
Central gray matter ^b						
Right	9.2	2.4	7.1	2.6	2.27	0.03
Left	8.3	2.2	6.6	2.6	2.01	0.05
Posterior gray matter ^b						
Right	8.5	2.3	8.0	2.1	0.59	0.56
Left	8.1	2.2	7.7	2.5	0.52	0.61

^aStudent's two-tailed *t* test; *df*=28 except for right-side temporal lobe total (*df*=27), right-side anterior gray matter (*df*=26), and left-side anterior gray matter (*df*=25).

^bAnterior=first temporal lobe slice, central=middle temporal lobe slice, posterior=last temporal lobe slice.

general linear models procedure of the Statistical Analysis System (11). To compare variables across diagnostic groups, *t* tests were used. Furthermore, a repeated measures MANOVA was performed to better examine the effects of side of structure. Associations among variables within each diagnostic group for the prefrontal region, temporal lobe, and lateral ventricles were assessed with Spearman rank order correlations.

RESULTS

Temporal Lobe

The volumes of the gray and white matter in the temporal lobe are listed in table 1. There was no significant difference in the number of slices through the temporal lobe between the control group and the schizophrenic patients (mean±SD=6.7±0.5 versus 6.5±0.6). The mean volume for the schizophrenic group was significantly smaller than that for the control group in the right temporal lobe (15%), right temporal lobe gray matter (18%), and left temporal lobe gray matter (21%). The distribution of the subjects' temporal lobe gray matter volumes is shown in figure 2. There was no significant difference between the patients and control subjects in white matter volume on either side of the temporal lobe. Thus, the difference in temporal lobe volume was attributable to the difference in gray matter volume.

When we examined the overall temporal lobe volumes with a MANOVA, taking all measurements into account, the difference between groups approached significance (*F*=2.49, *df*=4, 25, Wilks lambda=0.71, *p*=0.07). When examined by means of post hoc ANOVAs, the mean left and right temporal lobe gray matter volumes of the schizophrenic patients were found to be significantly smaller (left: *F*=5.87, *df*=1, 28, *p*=0.02; right: *F*=6.71, *df*=1, 28, *p*=0.02). In addition, a significant interaction between measure (gray and white matter volumes) and diagnostic group was found (*F*=6.64, *df*=1, 28, Wilks lambda=0.81, *p*=0.02).

The anterior, central, and posterior subdivisions of the temporal lobes of the two diagnostic groups were compared with *t* tests (see table 1). The schizophrenic patients had significantly smaller gray matter volumes in the right (23%) and left (20%) central sections, anatomically corresponding to the portions of the temporal lobe containing the amygdala and anterior hippocampus.

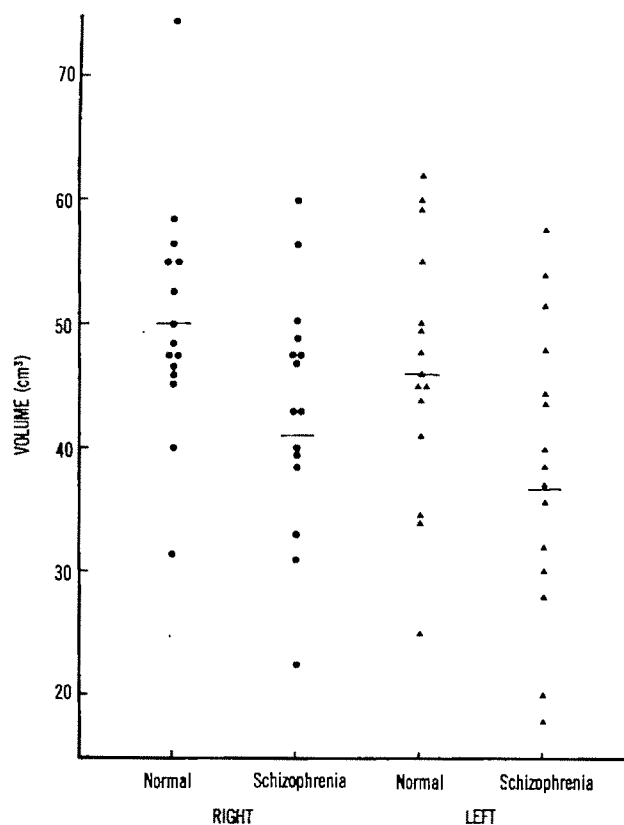
To determine whether there was an effect for side, the left and right gray and white matter volumes were used as dependent variables in a repeated measures MANOVA (two groups by two sides by two measures). There was a main effect for side, indicating that the right temporal lobe was significantly larger than the left temporal lobe in both groups (*F*=9.4, *df*=1, 28, Wilks lambda=0.75, *p*=0.005).

There was no significant difference in the degree of right-left asymmetry between the patients and control subjects, i.e., there was no Diagnosis by Side interaction (*F*=1.27, *df*=1, 27, Wilks lambda=0.96, *p*=0.27).

Prefrontal Lobe

The gray and white matter volumes in the prefrontal region are listed in table 2. There were no significant differences between the patients with schizophrenia and the normal control subjects in total, gray matter, or white matter volume according to two-tailed *t* tests.

A MANOVA was performed with the left gray matter volume, left white matter volume, right gray matter volume, and right white matter volume as dependent variables. There was no difference between the groups on the overall MANOVA (*F*=0.39, *df*=4, 26, Wilks lambda=0.94, *p*=0.82). The groups did not differ on any of these variables according to post hoc *t* tests. To determine whether there was a main effect for side, a repeated measures MANOVA (two groups by two sides by two measures) was performed. There was a significant main effect for side (*F*=11.78, *df*=1, 29, Wilks lambda=0.71, *p*=0.0018), indicating that the right prefrontal volume was larger than the left prefrontal volume. There was no significant difference in the degree of right-left asymmetry between the patients and the control subjects, i.e., there was no Side by Diagnosis interaction (*F*=0.38, *df*=1, 29, *p*<0.54).

FIGURE 2. Temporal Lobe Gray Matter Volumes of 15 Schizophrenic Patients and 15 Age- and Sex-Matched Normal Control Subjects^a

^aHorizontal lines indicate mean values.

Temporal and Prefrontal Correlations

Spearman correlations were performed to determine the correlations among the temporal and prefrontal gray and white matter volumes in the control and patient groups. In general, the diagnostic groups did not systematically differ. Within each diagnostic group, right gray matter correlated highly ($r_s > 0.74$, $p < 0.002$) with left gray matter in both the prefrontal ($N=17$) and temporal ($N=15$) lobes. In the prefrontal lobe, right and left white matter also correlated highly ($r_s > 0.81$, $p < 0.0002$) within each diagnostic group. In the temporal lobe, right and left white matter correlated highly ($r_s = 0.85$, $p = 0.0001$) within the patient group yet failed to correlate ($r_s = 0.30$, $p = 0.27$) within the control group. None of the variables age, height, sex, or rater correlated significantly with any volumetric measurement.

Lateral Cerebral Ventricles

The volumes of the lateral cerebral ventricles are shown in table 3. The mean total volume was 67% larger in the patient group. The volumes of the left and right lateral cerebral ventricles were 65% and 67% larger, respectively. A repeated measures ANOVA

TABLE 2. Prefrontal Region Volumes of 17 Schizophrenic Patients and 17 Age- and Sex-Matched Normal Control Subjects

Measure	Volume (cm ³)				t ^a	p
	Control Subjects		Schizophrenic Patients			
	Mean	SD	Mean	SD		
Gray matter						
Right	29.8	9.1	27.7	7.6	0.68	0.51
Left	29.0	6.9	27.4	8.1	0.61	0.55
White matter						
Right	30.7	10.3	32.1	14.1	0.33	0.75
Left	28.1	8.0	27.7	10.8	0.12	0.91
Total prefrontal region						
Right	60.5	14.7	59.8	18.8	0.15	0.88
Left	57.1	13.6	55.1	17.8	0.44	0.66
Right plus left	117.6	27.5	114.9	36.1	0.30	0.77

^aStudent's two-tailed *t* test; *df*=32.

showed a significant difference only between diagnostic groups; the patient group had larger ventricles ($F=5.52$, $df=1, 28$, $p=0.03$). When examined separately with ANOVA post hoc contrasts, both the right and left lateral ventricles differed significantly between diagnostic groups (see table 3).

We found no evidence of asymmetry of the lateral ventricles. There was no main effect for side ($F=0.42$, $df=1, 28$, Wilks lambda=0.99, $p=0.52$) and no Side by Diagnostic Group interaction ($F=0.02$, $df=1, 28$, $p=0.88$). Within each diagnostic group the volume of the lateral ventricles did not correlate with the volume of gray or white matter in either the prefrontal region or the temporal lobe.

To control for possible confounding effects of non-pathological variations in brain size, a corrected lateral ventricular volume was derived by dividing the total lateral ventricular volume by the total prefrontal volume. Prefrontal volume was chosen as a normalization parameter since no significant difference in this region was found between the normal control subjects and the patients with schizophrenia. (Total brain volume was not available as a reference since our scanning procedure did not include the last 1 to 2 cm of the posterior cerebrum.) In the patients ($N=15$), left temporal gray matter volume correlated significantly with corrected lateral ventricular volume ($r_s = -0.54$, $p < 0.04$) and right temporal gray matter volume showed a trend in that direction ($r_s = -0.47$, $p < 0.08$). In the control group, no such relationship was found. Neither uncorrected nor corrected lateral ventricular volume correlated with temporal lobe white matter volume in either diagnostic group.

DISCUSSION

Temporal Lobe

In this quantitative MRI study, temporal lobe gray matter volume was 20% smaller in patients with schizophrenia than in normal control subjects. While a

TABLE 3. Lateral Ventricular Volumes of 15 Schizophrenic Patients and 15 Age- and Sex-Matched Normal Control Subjects^a

Measure	Volume (cm ³)				Comparison ^b
	Control Subjects		Schizophrenic Patients		
	Mean	SD	Mean	SD	
Right	5.7	2.1	9.5	5.5	F=6.09, df=1, 28, p=0.02
Left	6.0	2.5	9.9	7.1	F=4.10, df=1, 28, p=0.05
Total	11.7	4.3	19.5	11.9	t=2.35, df=28, p=0.02

^aSignificant group effect according to repeated measures ANOVA test of hypothesis (F=5.52, df=1, 28, p=0.03).

^bANOVA post hoc contrast or Student's two-tailed t test.

smaller whole temporal lobe volume was also noted, this was accounted for by the smaller gray matter volume. There were no significant differences between the patients and control subjects in white matter volume in either temporal lobe. Smaller temporal lobe gray matter volume was most pronounced in the central section, anatomically corresponding to the part of the temporal lobe containing the amygdala and anterior hippocampus.

Our finding is consistent with the results of several post-mortem studies, in which structural brain abnormalities in schizophrenia were found. Bogerts et al. (3) used material derived from the Vogt collection and found smaller than normal volumes of several limbic temporal lobe structures, including the amygdala, hippocampus, and parahippocampal gyrus. Brown et al. (2) compared schizophrenic patients with patients who had affective disorder and found that the schizophrenic patients had 97% larger temporal horns (but only 19% larger lateral ventricles) and thinner parahippocampal cortices. While no overall difference in temporal lobe coronal area was noted, Brown et al. studied only a single slice, taken at the level of the interventricular foramen. While both of these studies implicate temporal lobe pathology, they do not distinguish the relative contributions of gray and white matter. The question of whether gray or white matter is preferentially affected has been addressed by Pakkenberg (6), who reported significantly, albeit diffusely, smaller volumes of cortical and central gray matter in 29 brains from patients with chronic schizophrenia. No significant difference in white matter volume was observed.

The process by which a selective reduction of gray matter could occur in patients with schizophrenia is unclear at present; however, progressive gray matter loss, as reflected by a decrease in the ratio of gray to white matter, has been studied in relation to normal aging. A range of gray to white matter ratios has been reported (12–14); the ratio depends on age range, diagnostic criteria, and measurement technique. What these studies confirm is a normal reduction in gray matter relative to white matter during the first 50 years of life. Katzman and Terry (15) have speculated that a relative reduction in gray matter with aging could result from a selective loss of small cortical neurons

without extracortical connections, i.e., interneurons. An alternative model for this process is neuronal shrinkage without axonal degeneration. Neuronal shrinkage with aging is supported by recent animal (16) and human (17) post-mortem studies. However, it is not known whether any of these processes occurs in schizophrenia. Smaller neuronal size, fewer total neurons, and other qualitative neuronal abnormalities have been observed in various regions in the brains of patients with schizophrenia (18). Yet factors such as diagnostic uncertainty, lack of adequate controls, and fixation changes make these often contradictory findings difficult to interpret. Another possibility is a disorder of neuronal development or migration with compensatory changes in axonal projections from normal neuronal populations that leaves white matter volume intact (19). With the availability of quantitative techniques and the use of matched control material, the nature of focal neuronal deficits in schizophrenia may be clarified.

We would like to emphasize that in our earlier MRI study (7), in which we used a manual planimetric technique, we did not find evidence of smaller temporal lobe volume in schizophrenia. This discrepancy may be due to the fact that the earlier method did not allow the separate quantitation of gray and white matter. Since the smaller temporal lobe volume in the current study was restricted to the gray matter, combining gray and white matter may have diluted the finding. Another possible explanation for the apparent inconsistency is that the samples may not have been comparable. As mentioned earlier, seven patients and 10 control subjects participated in both studies. When the mean temporal lobe gray matter volume and the mean lateral ventricular volume of the overlapping and nonoverlapping groups from the present study were compared by means of t test, no significant differences were found in the mean volumes of these two structures. We also performed a MANOVA to assess interaction between the overlapping and nonoverlapping groups, and no significant effect was observed (F=1.16, df=8, 16, Wilks lambda=0.63, p=0.38). Thus, it is unlikely that differences between the samples explain our inability to demonstrate abnormally small temporal lobe volume in the earlier study. An additional factor may have been a gain in sensitivity through the use of a computerized analysis system.

Several potential sources of error in deriving area measurements from MRI should be considered in a discussion of our findings. One source of errors is the variability in image density, or contrast, which is related to such factors as pulse sequence and alterations in relaxation time. As demonstrated by Zhu et al. (20), however, the use of an edge detection technique, as employed in our study, minimizes errors caused by such contrast variation. A second source of error is the spatial distortion produced by magnetic field inhomogeneity. Images from coronal and sagittal planes were found to be most susceptible to spatial distortion, particularly toward the periphery of the image (20). Spa-

tial distortion can magnify or reduce different regions of the imaging field. Measuring an object of known volume (a phantom) was recommended by Zhu et al. to correct for potential spatial distortion. More recently, Jack et al. (21) have suggested that the use of simple phantoms is not a good predictor of the kinds of measurement errors which occur when more geometrically complex shapes, such as the convexities of the temporal lobes, are measured. Since our method did not employ a phantom correction, the volumetric measures we report may be subject to error. Nevertheless, we feel it is unlikely that a systematic spatial distortion would affect one group of subjects more than the other. Since all subjects were examined with the same MRI scanner and with the same pulse sequence, any systematic spatial distortion should affect both groups equally and would not alter our finding of bilaterally smaller temporal lobe gray matter volume in patients with schizophrenia. Jack et al. have examined the effect of several MRI variables on the accuracy of volume measurements of phantom objects, including phase-encoding views, number of repetitions, slice width, variability over time (once a week for 4 weeks), and image field position (right or left). The accuracy fell within a 9% range when based on comparisons to a temporal lobe specimen with a volume determined by using the Archimedes principle.

Prefrontal Region

Finding comparable prefrontal gray matter volumes in the patients and control subjects was surprising in light of previous CT studies suggesting larger frontal cortical sulci in patients with schizophrenia (22, 23). Moreover, there has been a convergence of evidence from studies of regional cerebral blood flow (24–27), brain metabolism (28, 29), and neuropsychological factors (30, 31) pointing toward frontal lobe dysfunction in schizophrenia. It is possible that further refinement in measurement techniques will demonstrate smaller prefrontal volume. On the other hand, the prefrontal region may not be anatomically compromised, or at least not to the same degree as the temporal lobe. Prefrontal physiological dysfunction could result from structural pathology in brain areas that communicate with the prefrontal cortex (32). We are uncertain as to why the CT finding of larger prefrontal sulci does not have a corresponding MRI finding of smaller prefrontal volume, but these prefrontal region results are consistent with those in our earlier study (7).

Cerebral Asymmetry

We found that the right prefrontal region and the right temporal lobe were significantly larger than the left in normal individuals and in patients with schizophrenia. In the prefrontal region, the right side was larger than the left in 13 of the 17 control subjects and 15 of the 17 patients. In the temporal lobe, the right side was larger than the left in 13 of 15 control subjects

and 14 of 15 patients. In the temporal lobe, both the gray and white matter were larger on the right side, while in the prefrontal lobe, only the white matter was larger on the right side.

Asymmetry of two temporal lobe structures, the planum temporale and Sylvian fissure, has previously been reported in normal subjects (33, 34). The planum temporale is usually larger on the left side. The Sylvian fissure has been reported to extend farther back on the left and to rise more steeply on the right. LeMay has reported that the right temporal lobe is larger than the left (35). A technique similar to our own was used by Jack et al. (21) to measure the temporal lobe volume in 25 normal subjects. They also found that the right temporal lobe was larger; the mean temporal lobe volumes were 59 cm³ on the right and 51 cm³ on the left. While those values for temporal lobe volume are 31% lower than the ones for the normal subjects in our study (right=85.6 cm³, left=74.1 cm³), this difference is undoubtedly related to a more posterior definition of the temporal lobe boundary in our study. We employed the most posterior aspect of the Sylvian fissure, while Jack et al. used the internal auditory canal as a landmark. To our knowledge, ours is the first report of temporal lobe volume asymmetry in a pathological population and the first to examine the relative contributions of gray and white matter to normal temporal lobe asymmetry.

Previous post-mortem (36) and CT (37, 38) investigations have reported that in normal subjects the right frontal lobe is larger than the left. In a post-mortem study of the Yakovlev Collection, Weinberger et al. (36) observed that in 32 of 40 cerebra (20 of which were from fetuses or infants), the volume of the right frontal region was larger than that of the left by an average of 13%. By comparison, in generating volume estimates with MRI, we found that the prefrontal region was larger on the right by 6% in the control subjects and 9% in the patients, while the temporal lobe was larger on the right by a mean of 16% in the control subjects and 13% in the patients. These results suggest that valid volume measurements are provided with this MRI technique. The results, however, do not support observations of reversal of normal asymmetry in some patients with schizophrenia (39–42). In discussing findings of asymmetry, it is also important to emphasize that the difference in temporal lobe gray matter was seen bilaterally and was not asymmetric. We did not find evidence of lateralized pathology, which has been reported by some others (2, 4).

Lateral Ventricles

We also found that the lateral cerebral ventricles of the patients with schizophrenia were significantly larger than those of the control subjects. Lateral ventricular volume was 67% larger in the patient group than in the control group. This result is similar to the 62% larger lateral ventricular volume reported in our earlier MRI study (7)

and replicates CT findings of abnormally large lateral ventricles in schizophrenia (1).

Uncorrected lateral ventricular volume failed to correlate with gray or white matter volume in either the temporal lobe or the prefrontal region. Moreover, the main finding of this study, smaller temporal lobe gray matter volume in schizophrenia, did not predict larger ventricular volume. There are a number of possible explanations for this lack of correlation. One is that the smaller gray matter volume is not responsible for the larger lateral ventricles. Another may be that our quantitative methods are still too insensitive. Since it is likely that many factors, in addition to the brain pathology of schizophrenia, affect ventricular size (e.g., normal genetic determinants, embryological events, coincidental birth or head traumas), it is possible that the specific component related to temporal pathology is obscured.

In an effort to control for some of the nonspecific factors that might contribute to ventricular volume variance, we attempted a "normalization" of ventricular volume by referencing it to a neutral brain region, i.e., a region not found to differentiate patients from control subjects. This exploratory approach did result in a significant correlation between corrected ventricular volume and left temporal lobe gray matter volume and a trend toward significance for right temporal lobe gray matter volume. No such correlations were observed in the control group, suggesting that the relationship between these variables is a reflection of an abnormal condition. This correlation will need to be replicated in a new sample.

Finally, it is interesting that the temporal lobe gray matter volume of the patients was 18.5 cm³ smaller than that of the control subjects, while lateral ventricular volume was only 7.8 cm³ larger. Moreover, the lateral ventricular volume of the normal control subjects was only one-eighth of their temporal lobe gray matter volume. Therefore, a difference of 7.8 cm³ in lateral ventricular volume represents a much greater relative difference (67%) than is seen in the temporal lobe gray matter (20%). Small differences in quantity of tissue are thus "amplified" as they are translated into relatively large differences in ventricular volume. This relative quantitative difference may illustrate why the lateral ventricles serve as a particularly sensitive and reliable marker of smaller volume in surrounding brain structures.

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HPA Axis Hyperactivity and Recovery From Functional Psychoses

William H. Coryell, M.D., and Mark Zimmerman, B.A.

Some patients with functional psychoses follow a chronic, deteriorating course and others recover; at present clinicians have essentially no established factors beyond diagnosis and chronicity to predict which course a psychotic patient might follow. Because data on diagnostic specificity suggested that the dexamethasone suppression test might provide another, much needed prognostic factor, the authors administered these tests to 98 consecutively admitted patients with nonmanic psychoses. High postdexamethasone cortisol levels (6 µg/dl or higher) at baseline predicted recovery from psychosis at 1 year, independent of episode chronicity and diagnosis. Diagnosis did not correspond well to test results but was itself an important predictor.

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It is widely accepted that patients with affective disorder are likely to recover, while those with schizophrenia are not. Although empirically justified, this assumption is complicated by several factors. First, proposed definitions for schizophrenia are numerous and the overlap between them is often minimal (1); the boundary between psychotic affective disorder and schizophrenia therefore varies markedly by diagnostic system. Second, within any given diagnostic system, typical outcomes are far from inevitable; some patients with affective disorder have a chronic course (2-4) and some patients with schizophrenia recover (5-7). This results in part from misdiagnosis; some patients who appear to clearly have schizophrenia eventually prove to have affective disorder, while the converse is true of some patients who initially appear to have definite affective disorder. On the other hand, diagnostic imprecision need not explain all surprising outcomes, since all diseases show prognostic variability.

Received April 8, 1988; revision received Sept. 6, 1988; accepted Sept. 22, 1988. From the Department of Psychiatry, University of Iowa. Address reprint requests to Dr. Coryell, Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

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These circumstances and the devastating consequences of a chronic psychosis make any nondiagnostic outcome predictor profoundly important. Only one such predictor, acuteness, is generally accepted as indicative of eventual recovery. This is reflected in several widely used diagnostic systems that actually require a certain chronicity for the diagnosis of schizophrenia. Although other nondiagnostic predictors have emerged from follow-up studies, none has come into wide acceptance.

Studies which appeared between 1978 and 1982 offered abundant evidence that the dexamethasone suppression test (DST) might fill this role (8). Since abnormal plasma cortisol escape from suppression by 1 or 2 mg of dexamethasone occurred in 40%-100% of patients with psychotic depression (105 of 172 patients in pooling studies, or 61%) but in only 0%-10% of schizophrenic patients, an abnormal DST result raises the probability that a psychotic patient does indeed have an affective disorder and, therefore, will eventually recover. Although many later studies found higher nonsuppression rates in schizophrenia (8, 9), these findings were never reconciled with the earlier ones that showed high diagnostic specificity. In particular, no one determined whether, as the earlier studies would suggest, nonsuppression predicts recovery from psychosis in a large, diagnostically mixed sample. The following describes a 1-year follow-up designed to do this.

METHOD

Consecutively admitted patients at the University of Iowa Psychiatric Hospital were invited to participate if they met the following criteria: 1) they exhibited delusions and/or hallucinations, 2) neither an organic psychiatric disorder (e.g., delirium, dementia, organic psychotic disorder) nor mania was included in the differential diagnosis, and 3) there were no conditions present that were believed to invalidate the results of either the DST or the thyrotropin-releasing hormone (TRH) stimulation test.

Within a week of admission, each patient ingested 1 mg of dexamethasone at 11:00 p.m. and provided plasma samples the following day at 8:00 a.m., 4:00 p.m., and 11:00 p.m. Cortisol levels were measured

by radioimmunoassay by using a specific cortisol antiserum produced in rabbits against cortisol-3-carboxymethyloxime, conjugated to bovine serum albumin and purchased from American Biosystems (St. Paul, Minn.). There was no cross-reactivity with dexamethasone, progesterone, testosterone, or 11-deoxycortisol. The intra-assay and interassay coefficients of variation were 12.2% and 11.1%, respectively, at concentrations near the cutoff to classify patients as nonsuppressors.

The following analyses use the highest of the three postdexamethasone cortisol levels for each individual. The most frequently used threshold to indicate nonsuppression has been 5 µg/dl, although values of 4, 4.5, and 6 µg/dl have also been used. We have elected here to designate an ambiguous range of 4–6 µg/dl, inclusive; values below and above this range indicate definite suppression and definite nonsuppression, respectively. We have also selected a threshold of 10 µg/dl, since this value best distinguished patients with psychotic depression from patients with nonpsychotic depression in an earlier series (10); other workers as well have found that psychotically depressed patients often have particularly high postdexamethasone cortisol values (11, 12).

The intake diagnostic procedure also occurred within 1 week of admission. After reviewing all available medical records, the second author completed the full Schedule for Affective Disorders and Schizophrenia (SADS) (13). The first author independently reviewed the same medical records and conducted an unstructured clinical interview designed to establish diagnoses in three systems, as described elsewhere (14). We then reached a consensus diagnosis, according to DSM-III.

The second author, who was blind to DST results, reinterviewed each patient at 6 months and again at 12 months following study intake. These interviews were patterned after the Longitudinal Interview Follow-Up Evaluation (15) used in an ongoing collaborative study of the affective disorders. Accordingly, each patient was assigned a set of scores to reflect psychopathology on a weekly basis. If the patient had experienced 8 or more consecutive weeks with neither delusions nor hallucinations and with full insight (he or she recognized previous psychotic experiences as such) and if this period was contiguous with the end of the 1-year follow-up, the patient was considered recovered from psychosis. A Global Assessment Scale (GAS) score (16) was assigned as well to describe both symptom level and psychosocial functioning for the week before the follow-up interview. A score above 90 on this 100-point scale indicated "superior functioning in a wide range of activities" and no symptoms whatsoever; a score between 31 and 40 indicated "major impairment in several areas, such as work, family relations, judgment, thinking or mood or some impairment in reality testing or communication or a single suicide attempt."

All treatment was naturalistically determined. Treatment was neither withheld nor interrupted pending the

DST or the diagnostic procedures, nor did the research protocol influence the length of hospital stay. However, treatment was carefully monitored and was coded according to conventions developed elsewhere (17). Thus, for each week of follow-up, all antipsychotic, benzodiazepine, tricyclic antidepressant, and monoamine oxidase inhibitor (MAOI) doses were reduced to chlorpromazine, diazepam, imipramine, and phenelzine equivalents, respectively. The doses of other psychotropic drugs were recorded unchanged, as were the number of ECTs received.

To detect artifacts we considered any variable that might influence both DST results and prognosis. The most obvious of these possibilities, of course, was diagnosis. Stress preceding the onset of psychosis predicts recovery, according to some studies (7), while, according to others, psychological stress can produce high rates of DST nonsuppression (18). We considered episode duration also, since acuteness has predicted recovery in many studies and, in at least two studies (19, 20), has been associated with DST nonsuppression. "Duration" was defined by SADS item 214 as the "best estimate of duration of this episode to date, from onset of first signs of change in usual condition to time of evaluation." Finally, weight loss, if of sufficient degree, induces DST nonsuppression (21) and, as a common depressive symptom, may have prognostic significance.

Analysis of variance and chi-square tests were used for three-way comparisons. Those resulting in significance levels less than 0.05 were followed by Newman-Keuls pairwise tests in the case of continuous variables and by additional chi-square tests in the case of categorical variables. Fisher's exact tests were used when any expected value was less than 5.

RESULTS

Of 98 consecutively admitted patients with functional psychosis, 90 (91.8%) were successfully reevaluated at 1 year; baseline DST results were unavailable for two of these. Of the remaining 88, 41 (46.6%) were clearly normal suppressors at baseline, while a third (34.1%) were clearly nonsuppressors (table 1). Patients grouped by low, intermediate, and high postdexamethasone cortisol levels did not differ significantly by any of the potentially confounding measures tested (tables 1 and 2). These patient groups also did not differ by mean doses of the various psychotropic agents given during the week before intake or by the likelihood of drug discontinuation before intake.

During follow-up, similar proportions received ECT or 8 or more weeks of treatment with antipsychotics, lithium, tricyclic antidepressants, MAOIs, or minor tranquilizers. Differences did emerge when patients were divided, instead, by outcome. The 36 patients who recovered were roughly twice as likely to have received at least 8 weeks of tricyclic antidepressant therapy (N=21, 58.3%) or lithium (N=17, 47.2%) as

TABLE 1. Baseline Characteristics and GAS Score 1 Year After Admission of 88 Psychotic Patients Who Were Given the DST

Patients' Postdexamethasone Cortisol Level at Intake	Age (years) ^a		Duration of Episode (weeks)		Degree of Stress Before Onset ^b		Weight Loss Before Admission ^c		GAS Score at 1 Year ^d	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<4 µg/dl (N=41)	33.8	9.7	281.1	328.6	2.8	1.7	2.5	1.6	47.0	16.3
4-6 µg/dl (N=17)	40.7	14.9	222.9	330.2	3.0	1.8	2.6	1.8	55.0	20.8
>6 µg/dl (N=30)	42.2	19.0	357.7	638.7	2.4	1.5	2.8	1.8	61.2	19.8

^aF=3.2, df = 2, 85, p<0.04.^bRating of 1 to 6; 1=none, 6=extreme.^cRating of 1 to 6; 1=none, 6=25 or more lbs.^dF=5.2, df=2, 85, p<0.007; significant difference between the group with levels <4 and >6 µg/dl, Newman-Keuls pairwise test.

TABLE 2. Baseline DSM-III Diagnoses and Recovery 1 Year After Admission of 88 Psychotic Patients Who Were Given the DST

Patients' Postdexamethasone Cortisol Level at Intake	Diagnosis ^a						Patients Recovered at 1 Year ^b	
	Women		Major Depression		Schizophrenia			
	N	%	N	%	N	%	N	%
<4 µg/dl (N=41)	21	51.2	21	51.2	17	41.5	10	24.3
4-6 µg/dl (N=17)	11	64.7	10	58.8	6	35.3	7	41.2
>6 µg/dl (N=30)	16	53.3	21	70.0	8	26.7	19	63.3

^aFive patients had neither disorder; diagnoses were schizoaffective disorder in three cases and paranoid disorder in two cases.^b $\chi^2=10.8$, df=2, p<0.005, pairwise significance.

TABLE 3. Diagnosis and Recovery Rate 1 Year After Admission of 86 Psychotic Patients Who Were Given the DST

Item	Major Depression With Mood-Congruent Psychotic Features (N=24) ^a		Schizoaffective Disorder or Major Depression With Mood-Incongruent Psychotic Features (N=31)		Schizophrenia (N=31)	
	N	%	N	%	N	%
Female	15	62.5	17	54.8	13	41.9
Postdexamethasone cortisol level at intake (µg/dl)						
<4	9		14		17	
Recovered	3	33.3	4	28.6	2	11.8
4-6 ^b	3		8		6	
Recovered	3	100.0	4	50.0	0	0
>6	12		9		8	
Recovered ^c	11	91.7	6	66.7	2	25.0

^aSignificant difference in recovery rate across the three groups (p=0.01, df=2, Fisher's exact test); significant difference between the groups with cortisol levels <4 and >6 µg/dl (p<0.01, Fisher's exact test).^bp=0.006, df=2, Fisher's exact test; significant difference between group with major depression with mood-congruent psychotic features and schizophrenic group (p=0.01).^cp=0.004, df=2, Fisher's exact test; significant difference between group with major depression with mood-congruent psychotic features and schizophrenic group (p<0.01).

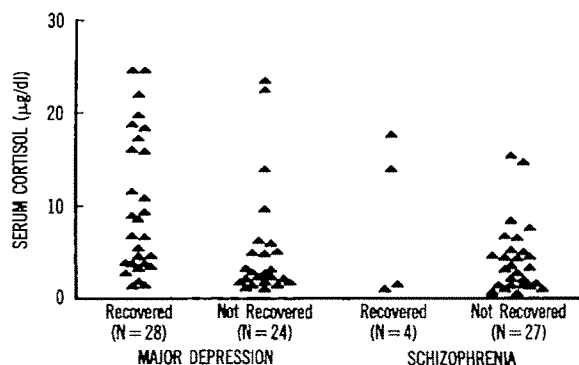
were the 52 patients who did not recover (N=18, 34.6%; and N=13, 25.0%, respectively). Conversely, patients who recovered were one-half as likely to have received antipsychotics for 8 or more weeks as were those who did not recover (N=16, 44.4% versus N=41, 78.8%).

High postdexamethasone cortisol levels markedly increased the likelihood of recovery with full insight at 1 year; patients who had clearly been nonsuppressors were more than twice as likely to recover than those who had been suppressors. Similarly, patients with low, intermediate, and high baseline postdexameth-

asone cortisol levels exhibited progressively higher GAS scores on follow-up.

As predicted, there was a relationship between baseline DST results and the likelihood of recovery among patients who had the inherently more heterogeneous diagnoses of schizoaffective disorder or depression with mood-incongruent psychotic features (table 3). However, this relationship held as well for patients with the more typical, mood-congruent psychotic depression. A similar relationship emerged among patients with schizophrenia, although recovery among these patients was too uncommon to yield a clear re-

FIGURE 1. Maximum Postdexamethasone Cortisol Level at Intake and Recovery From Psychosis During 1-Year Follow-Up of 83 Patients With Major Depression or Schizophrenia



relationship, even if it indeed existed. Moreover, diagnosis was clearly related to outcome regardless of baseline DST result. The mean \pm SD ages for the three groups—major depression with mood-congruent psychotic features, schizoaffective disorder or major depression with mood-incongruent psychotic features, and schizophrenia—were 41.6 ± 17.4 , 36.0 ± 12.8 , and 36.3 ± 13.4 years, respectively. The mean \pm SD duration of episode at intake for the three diagnostic groups was 63.0 ± 161.0 , 119.1 ± 137.8 , and 604.4 ± 543.5 weeks, respectively; the difference between the schizophrenic group and the other two groups was significant ($F=21.5$, $df=2$, 83 , $p=0.0001$; Neuman-Keuls, comparison between group with major depression with mood-congruent psychotic features and group with schizophrenia and between group with schizoaffective disorder or major depression with mood-incongruent psychotic features and group with schizophrenia).

When we omitted patients with intermediate postdexamethasone cortisol levels of 4–6 $\mu\text{g/dl}$, nonsuppression had a sensitivity to subsequent recovery of 65.5%—19 of the 29 who recovered were nonsuppressors at intake. The specificity of a negative test (postdexamethasone cortisol level less than 4 $\mu\text{g/dl}$) was 73.8%—of the 42 who did not recover, 31 were normal suppressors. The likelihood that a patient with a positive test would go on to recover (positive predictive value) was 63.3%; this rose to 72.2% with a nonsuppression threshold of more than 10 $\mu\text{g/dl}$. This higher threshold seemed particularly important for schizophrenic patients; of those with cortisol levels above 10 $\mu\text{g/dl}$, two of four (50%) recovered, compared to two of the 27 (7%) with lower values ($p=0.070$, Fisher's exact test) (figure 1).

Although none of the potentially confounding variables were significantly associated with baseline DST results (table 1), two of them, diagnosis and duration at intake, were significantly associated with outcome, both in the expected directions (table 4). We therefore entered these variables into regression analyses along with postdexamethasone cortisol values. With the remaining two variables controlled, only postdexameth-

asone cortisol level significantly predicted 1-year GAS scores, while both postdexamethasone cortisol levels and diagnosis significantly predicted recovery from psychosis.

These data, then, suggest a stepwise approach to prediction. Only four of 31 schizophrenic patients (12.9%) were recovered at 1 year. The likelihood of recovery increased threefold (eight of 24 or 33.3%) for nonschizophrenic patients with normal DST results at intake (postdexamethasone cortisol levels less than 4 $\mu\text{g/dl}$) and fivefold (23 of 33 or 69.7%) for nonschizophrenic patients with abnormal DST results at intake.

DISCUSSION

Widespread use of the DST to determine prognosis should await successful replication across at least several other centers. Thus far, only one study has explored neuroendocrine test results in a similar way, and it reached similar conclusions. Targum (22) described a small group of patients with schizophreniform psychosis and found that abnormal results on either the DST or the TRH stimulation test were associated with recovery. The present data extend to a larger, more diagnostically mixed, and representative sample of psychotic patients.

DST results have clearly separated schizophrenic patients from affective disorder patients in some studies and have failed to do so in others (8). When designing the present study, we suspected that at least some of these failures had resulted from diagnostic inadequacies—a lack of sensitivity to affective symptoms, the failure to adequately use informants and medical records, and/or a lack of thoroughness in assessing psychopathology. Since we designed the present study to assiduously avoid these shortcomings, we predicted that nonsuppression would clearly separate schizophrenic patients from patients with major depression with mood-congruent psychotic features. Accordingly, we expected the relationship between nonsuppression and recovery to emerge primarily in the more diagnostically ambiguous group of patients with schizoaffective disorder or depression and mood-incongruent psychotic features. Instead, the relationship between nonsuppression and recovery was as strong or stronger among patients who had only mood-congruent psychotic features. Diagnostic imprecision may explain some of these findings; some patients with mood-congruent psychotic features and low postdexamethasone cortisol levels may eventually prove to have schizophrenia, and additional schizophrenic patients with initially high postdexamethasone cortisol levels may eventually recover. An extended follow-up is in progress to determine these possibilities. However, some additional factor linking initial DST results and subsequent recovery must be assumed in the meantime. Perhaps this factor gives rise to both psychosis and hypothalamic-pituitary-adrenal (HPA) axis disturbance when the psychosis is at an imminently reversible

TABLE 4. Linear Regression Analysis of the Effect of Diagnosis, Episode Duration, and Postdexamethasone Cortisol Level on Outcome of Psychotic Patients 1 Year After Admission

Item	N	GAS Score at 1 Year				Recovery at 1 Year			
		R	F	df	p	R	F	df	p
Single regression									
Log postdexamethasone cortisol level	88	0.34	10.9	1, 84	0.001	0.32	9.7	1, 84	0.002
Duration at intake	90	-0.33	10.9	1, 86	0.001	-0.23	5.1	1, 86	0.027
Diagnosis ^a (1=major depression, 2=schizophrenia)	92	-0.40	16.1	1, 88	0.001	-0.51	29.4	1, 88	0.001
Multiple regression, overall ^a	83	0.50	8.8	3, 79	0.001	0.56	12.4	3, 79	0.000
Log postdexamethasone cortisol level		0.31	8.4	1, 79	0.005	0.26	5.9	1, 79	0.017
Duration at intake		-0.15	1.8	1, 79	0.19	-0.01	0.003	1, 79	0.95
Diagnosis ^a (1=major depression, 2=schizophrenia)		-0.21	3.8	1, 79	0.06	-0.41	15.8	1, 79	0.001

^aExcludes six patients who had neither major depression nor schizophrenia.

stage. This factor may gradually cease to disturb HPA function if the psychosis becomes relatively persistent or irreversible, whatever the underlying illness.

Postdexamethasone cortisol levels were far from perfect outcome predictors in this study, nor do infallible outcome predictors exist in medicine. However, we know of no single factor in psychiatry found to be more strongly related to outcome unless it be diagnosis. Pending replication, then, the DST may join diagnosis as a critical tool with which to anticipate the course of functional psychosis.

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Clinical Status and Emotional Adjustment of Children of Depressed Mothers

Catherine M. Lee, Ph.D., and Ian H. Gotlib, Ph.D.

The authors compared children (ages 7–13 years) of unipolar depressed mothers with children of nondepressed psychiatric patients, of nondepressed medical patients, and of nondepressed mothers in the community. The children's adjustment was rated by clinicians on the Child Adjustment Schedule and by the mothers on the Child Behavior Checklist. The highest proportion of clinically significant problems was found in the children of the depressed mothers. However, the overlap between the problems of these children and those of the children of the nondepressed psychiatric patients calls into question the formulation that children's adjustment difficulties are specific to parental depression. (Am J Psychiatry 1989; 146:478–483)

There has been increasing concern that the offspring of parents with affective disorders may be at risk for adjustment difficulties (1, 2). Addressing this issue, a number of studies have assessed depressed parents' perceptions of their children's functioning. Billings and Moos (3), for example, found that depressed parents reported a greater number of physical and psychological problems in their children than did nondepressed parents. Similarly, Weissman et al. (4) found, on the basis of parents' reports, that more of the children of depressed parents than of nondepressed parents evidenced psychiatric symptoms and met the criteria for various *DSM-III* disorders. Although these are important data, they must nevertheless be considered preliminary, because they were based on the perceptions of depressed parents rather than on professional observations or assessments of the children. Because depressed parents' reports may be biased by a tendency to see both their parenting and their chil-

dren's behavior in negative light (5), it is important to consider studies that have assessed the functioning of children of depressed parents in a more objective manner.

On the basis of direct interviews with children, a number of studies have reported a high rate of affective disorders in the offspring of depressed patients (6, 7). However, because these studies compared children of depressed parents with children of nonpsychiatric control subjects, the question of whether children's observed adjustment difficulties are specific to parental depression remains at issue. Recently, investigators have compared children of depressed parents with offspring of parents exhibiting nondepressive as well as nonpsychiatric disorders. For example, Hirsch et al. (8) compared the adolescent children of unipolar depressed parents with the offspring of arthritic parents and nondepressed parents in the community. Although the children of the depressed parents reported a greater number of symptoms than did the children of parents in the community, the children of the depressed parents did not differ from the children of the arthritic parents on any of the measures. It is important to note that Hirsch et al. did not assess the psychological adjustment of the arthritic parents. Given the high frequency of depressive symptoms in rheumatoid arthritis patients (9), one cannot rule out the possibility that the lack of differences between the children of depressed parents and those of arthritic parents was attributable to the presence of depression in the arthritic parents rather than to the effects of general parental disability on child adjustment.

Addressing this issue, Hammen et al. (10, 11) assessed psychopathology in unipolar depressed, bipolar depressed, medically ill, and normal mothers as well as in their children. Compared with the children of normal mothers, the children of depressed mothers evidenced high rates of psychiatric diagnoses. Interestingly, some of the medically ill parents in this study also reported a history of psychopathology, and the children of this group of parents also had moderate rates of psychiatric diagnoses, although they were lower than the rates in the children of parents with affective disorders. Moreover, when psychosocial stresses were covaried, group differences were attenuated. Hammen et al. concluded that maternal depressive symptoms

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and ongoing strains both have an important effect on child adjustment.

In sum, although the studies we have reviewed provide promising evidence of a link between parental depression and children's difficulties, methodological shortcomings have left two important issues unaddressed. First, whether children's adjustment difficulties are specific to parental depression remains at issue. The results of recent studies suggest that general parental disability and psychological distress may be equally plausible explanations for the observed adjustment problems. Second, reports by depressed women may reflect a negative response bias rather than an accurate perception of their children as disturbed, and it is imperative that the children be assessed directly.

The present study was designed to address these issues by examining the adjustment of children of groups of mothers who were unipolar depressed psychiatric patients, nondepressed psychiatric patients, nondepressed medical patients, and nondepressed, non-medical control subjects in the community. The inclusion of three groups other than depressed patients permitted an evaluation of several hypotheses. The depression specificity hypothesis (1) predicts that there will be a higher proportion of child adjustment problems in the offspring of depressed patients than in the children of the three nondepressed groups. The psychological distress hypothesis (10-12) predicts that children's difficulties will be related to maternal psychopathology and to psychological distress in general; thus, the children of the two psychiatric groups would be expected to evidence poorer adjustment than the children of the two nonpsychiatric groups. Finally, the general disability hypothesis (8) predicts that children's problems will be associated with maternal physical and psychological disorder; thus, children's difficulties would be expected to be evident in all three groups of patient mothers.

To determine whether depressed mothers' reports of their children's difficulties are due to a maternal negative response set or represent accurate perceptions, information concerning the children's adjustment was obtained through the use of multiple measures completed by multiple informants. The negative response set hypothesis (13) predicts that although depressed mothers will evaluate their children negatively, blind ratings by clinicians will fail to corroborate the mothers' impressions. In contrast, the child vulnerability hypothesis (10, 11) predicts that both clinicians and mothers will identify adjustment problems in the children.

METHOD

The sample in this study consisted of 71 mother-child dyads. Each child was between the ages of 7 and 13 years, and each mother was the child's biological parent. Four groups of dyads were formed: 1) 20 dyads in which the mothers were currently receiving outpatient psychiatric treatment for unipolar depression,

2) 13 dyads in which the mothers were currently receiving outpatient treatment for psychiatric disorders other than depression, 3) eight dyads in which the mothers were currently receiving outpatient treatment for a medical condition (arthritis), and 4) 30 dyads in the community in which the mothers were not receiving outpatient treatment for either emotional or physical problems.

We recruited the mothers in the three patient groups from medical and psychiatric treatment facilities in the London, Ontario, area. Potential subjects were given letters from their therapists or physicians that outlined the study. The names of those women who expressed interest in the study were passed on to a research assistant, who telephoned the women to provide them with additional information. Control subjects in the community were recruited through newspaper advertisements soliciting participants in a study of mother-child relationships. Given these recruitment procedures, which were designed to protect the patients' confidentiality and to avoid coercion to participate, it is not possible to calculate response rates. It is our impression that the psychiatric patients who agreed to participate may represent a less disturbed sample of the population of female psychiatric outpatients. The probable consequence of such a selection bias would be to attenuate differences between the psychiatric and nonpsychiatric groups. Finally, pain ratings made by the arthritic women who participated in the study indicated that the severity of their discomfort was comparable to that of women from the same clinic who declined to participate.

For a mother and child to be considered for inclusion in the study, they had to have lived together for at least a year. In addition, in order to obtain a relatively homogeneous sample that was uncontaminated by the effects of alcoholism, psychosis, or organicity, mothers were excluded from the study if they demonstrated evidence of alcoholism, psychotic ideation, or brain damage. Finally, the youngest child in the family whose age was between 7 and 13 years was selected for participation in the study.

Measures

Maternal functioning. Because there is often a low degree of concordance between clinical ratings and self-report measures of depression (14, 15), multiple measures were used to assess subjects' depression. All of the mothers completed the Beck Depression Inventory (16), a 21-item self-report measure of the depth or intensity of depression. In addition, potential patients/subjects were assessed by a clinical psychology doctoral student (C.M.L.) on the Hamilton Rating Scale for Depression (17), a 17-item clinician-rated measure of depression, and according to the criteria for a *DSM-III* diagnosis of major affective disorder. The assessment interviews were audiotaped and subsequently rated by a clinical psychologist (I.H.G.) in order to establish diagnostic reliability. The two raters attained

perfect agreement in the diagnosis of subjects as depressed or nondepressed, indicating that the diagnoses were made reliably.

Group assignment for the psychiatric patients was based on *DSM-III* diagnoses of depression and scores on the Hamilton depression scale. Specifically, a psychiatric outpatient was classified as depressed if she 1) met the *DSM-III* criteria for a diagnosis of major depressive episode or dysthymic disorder and 2) evidenced moderate to severe levels of depression, defined as a minimum score of 14 on the Hamilton depression scale. Patients with previous manic episodes were not included in the study. A psychiatric outpatient was classified as nondepressed if she 1) had no history of previous psychiatric treatment for depression, 2) failed to meet the *DSM-III* criteria for a diagnosis of major affective disorder, and 3) obtained a score of 10 or less on the Hamilton scale. The majority of the nondepressed psychiatric outpatients were diagnosed as manifesting symptoms of anxiety disorder, personality disorder, and adjustment disorder (without depressed mood). Criteria for inclusion in the group of medical outpatient mothers were 1) no reported current or past treatment for a psychiatric disorder, 2) failure to meet the *DSM-III* criteria for a diagnosis of major affective disorder, and 3) a Hamilton depression score of 10 or less. Community subjects were accepted into the study if they had no history of psychiatric disorder and obtained a score of less than 10 on the Beck inventory.

Following the semistructured interview, each patient was also assessed on the Global Assessment Scale (GAS) (18) to provide a rating of her overall level of functioning. The GAS values range from 1, representing the hypothetically sickest individual, to 100, the hypothetically healthiest. Endicott et al. (18) have reported good interrater reliability and have presented data indicating that the GAS may be useful in identifying former psychiatric inpatients who are at high risk for relapse.

Child functioning. The children's functioning was assessed by means of an interview with the child and by maternal ratings. The children were interviewed with the Child Assessment Schedule (19), a semistructured protocol designed for the clinical assessment of children 7 years of age and older. This schedule includes assessment of fears and anxieties, worries and concerns, self-image, mood disturbance, physical complaints, and conduct problems. Hodges et al. (19, 20) have reported promising initial psychometric data for the schedule. In the present study, interrater reliability was determined by having a second rater code audiotapes of 15 of the Child Assessment Schedule interviews. Kappa coefficients calculated on the total symptom scores for each subscale of the schedule ranged from 0.96 to 1.0, indicating a high degree of reliability between raters. Following administration of the Child Assessment Schedule, the interviewer assigned a rating on the Global Assessment Scale for Children (21), an adaptation of the adult GAS. Acceptable interrater re-

liability and discriminant validity have been reported for this measure (22).

All of the mothers also completed the Child Behavior Checklist (23), on which behavior problems are rated in terms of the most apt descriptions of the child's behavior over the previous 6 months. Achenbach and Edelbrock (24) used raw scores obtained from 1,300 parents of normal children to compute normalized T scores for each of the scales of the checklist; they have also reported adequate construct validity and criterion validity. Children's scores can be defined as "clinical" or "nonclinical" on the basis of T scores indicating problems at the 90th percentile (25), and we used this dichotomizing procedure in the present study.

Procedure

A research assistant (who remained blind to the subjects' group assignments) contacted those subjects who met the inclusionary criteria and made arrangements for mothers and children to attend a research session within 1 week of the mothers' assessment interviews. Upon arrival at the laboratory, the mothers were given a detailed written overview that described the procedures of the study and were assured of confidentiality. The procedures were also described to the children, and data collection began only after both mothers and children consented to the procedures. The mother was taken to a separate room and was asked to complete a packet of questionnaires that included the Beck inventory and the Child Behavior Checklist. During this time, the child was assessed on both the Child Assessment Schedule and the GAS for Children by a trained interviewer who was blind to the group assignment of the dyad. Finally, the research assistant thanked the mother and paid her \$15 (Canadian) and answered any questions.

RESULTS

A multivariate analysis of variance (MANOVA) conducted on the mothers' age, income, years of education, number of children, and the age of the children being assessed revealed no main effect for group ($F=1.59$, $df=15, 157$, $p>0.05$), indicating that the mothers in the four groups did not differ significantly with respect to demographic variables.

Maternal Functioning

Mothers in each of the three patient groups (depressed and nondepressed psychiatric, and medical) were assessed on the GAS. Their mean scores are presented in table 1. An analysis of variance (ANOVA) revealed a main effect for group. Subsequent Newman-Keuls post hoc comparisons revealed that the medical patients were rated as functioning at a significantly higher level of adjustment than the nondepressed psy-

TABLE 1. Scores on Measures of Adjustment of Depressed and Nondepressed Mothers and Their Children^a

Mothers' Group	Mothers' Score				Children's Score			
	GAS ^b		Beck Inventory ^c		Child Assessment Schedule ^d		GAS for Children ^e	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Depressed psychiatric patients (N=20)	49.9 _a	8.3	19.8 _a	10.1	12.9 _a	6.4	62.7 _a	7.1
Nondepressed psychiatric patients (N=13)	60.8 _b	4.7	9.1 _b	6.2	12.5 _a	6.6	66.3 _a	11.2
Nondepressed medical patients (N=8)	74.0 _c	5.0	7.9 _b	4.8	7.9 _{a,b}	5.0	77.1 _b	4.6
Nondepressed women in the community (N=30)	—	—	3.9 _b	3.2	6.0 _b	4.5	78.9 _b	6.9

^aMeans for the same measure that have different subscripts were significantly different at the $p < 0.05$ level (Newman-Keuls tests).

^bGAS=Global Assessment Scale; higher score indicates better functioning. Significant group effect ($F = 34.5$, $df = 2, 37$, $p < 0.0001$).

^cHigher score indicates more intense depression. Significant group effect ($F = 23.9$, $df = 3, 70$, $p < 0.0001$).

^dHigher score indicates more fears, worries, physical complaints, etc. Significant group effect ($F = 7.9$, $df = 3, 70$, $p < 0.001$).

^eHigher score indicates better functioning. Significant group effect ($F = 20.9$, $df = 3, 70$, $p < 0.0001$).

TABLE 2. Children of Depressed and Nondepressed Mothers Who Had Child Behavior Checklist Scores in the Clinical Range

Mothers' Group	Children With Scores in the Clinical Range ^a			
	Internalizing Factor		Externalizing Factor	
	N	%	N	%
Depressed psychiatric patients (N=20)	13	65.0	13	65.0
Nondepressed psychiatric patients (N=13)	4	30.8	5	38.5
Nondepressed medical patients (N=8)	0	0.0	0	0.0
Nondepressed women in the community (N=30)	7	23.3	4	13.3

^aSignificant difference between groups ($\chi^2 = 17.3$, $df = 3$, $p = 0.0006$).

chiatric patients, who in turn were rated as functioning at a higher level than the depressed psychiatric patients.

The mothers' mean scores on the Beck inventory are also presented in table 1. An ANOVA on these scores similarly revealed a significant group effect. Newman-Keuls comparisons revealed that the Beck inventory scores of the depressed mothers were significantly higher than those of the mothers in the other three groups; there were no significant differences between the mothers in the three nondepressed groups.

Child Functioning

To compare the rates of child disturbance in the four groups, we examined the proportions of children in each group whose behavior, as rated by their mothers on the Child Behavior Checklist, exceeded an empirically established clinical cutoff score. As described earlier, children's scores were defined as "clinical" or "nonclinical" on the basis of T scores on the Child Behavior Checklist that indicated problems at the 90th percentile (see table 2). Groups differed significantly in the proportions of children whose behavior was rated within the clinical range. For both internalizing and externalizing problems, the highest proportions of clinical-range scores were found for the children of the depressed mothers; indeed, two-thirds of these chil-

dren were placed in the clinical range on the Child Behavior Checklist. As can be seen from table 2, no child of a mother in the medical patient group was rated as functioning in the clinical range.

Having established that a high proportion of depressed mothers rated their children as demonstrating substantial adjustment difficulties, we then examined clinicians' blind ratings of these children. The children's mean total symptom scores on the Child Assessment Schedule and their ratings on the GAS for Children are presented in table 1. A MANOVA conducted on these two measures yielded a significant group effect ($F = 9.0$, $df = 6, 132$, $p = 0.001$). Univariate analyses indicated that this effect was significant for the Child Assessment Schedule total scores and for the scores on the GAS for Children. Newman-Keuls comparisons indicated that, consistent with the maternal ratings, interviewers identified a greater number of symptoms and poorer overall adjustment in the children of both the depressed and the nondepressed psychiatric patients than they did in the children of the mothers in the community; the children of the medical patients did not differ significantly from the children in the other three groups with respect to their Child Assessment Schedule scores and did not differ from the children of the community mothers with respect to their scores on the GAS for Children. In comparison with the mean ratings on the Child Assessment Schedule presented by Hodges et al. (19), it is apparent that the children of both the depressed and the nondepressed psychiatric patients in the present study were functioning at a level comparable to a group of behaviorally disordered outpatient children.

DISCUSSION

Using multiple measures, we assessed the adjustment of children of depressed mothers. To determine whether the children's adjustment difficulties were specific to depression in the mothers, children of nondepressed psychiatric patients and medical patients were also assessed. The results of this study indicate that two-thirds of the children of depressed mothers were

described by their mothers as functioning within the clinical range of behavior problems. In contrast, none of the medical patients rated their children in the clinical range; the proportion of nondepressed psychiatric patients who identified their children as functioning within the clinical range was intermediate, between the community and depressed groups.

The clinicians' ratings also identified a considerable number of adjustment difficulties in the children of mothers who were psychiatric patients. Considered collectively, the present results corroborate previous findings of impairment in the children of emotionally disturbed parents (3, 4, 6, 7, 10, 11). Moreover, the present data extend these findings by indicating that the reported impairments were not a function of a depression-related maternal negative response set but were also evident to interviewers who were blind to maternal diagnostic status.

Equally important, the present findings call into question the idea that poor adjustment in children is specific to maternal depression. Children of both the depressed and the nondepressed psychiatric patients were rated by interviewers as demonstrating impaired functioning. In contrast, the children of the medical patients did not differ on these measures from the children of the community control subjects. These data lend support to the psychological disturbance hypothesis (10–12), since the children of both depressed and nondepressed psychiatric patients demonstrated greater difficulties than did the children of medical patients and women in the community.

The absence of statistically significant differences in the adjustment of the children of medical patients and the children of women in the community stands in contrast to the results reported by Hirsch et al. (8) for a sample of adolescents. It is possible that this discrepancy reflects differences in the ages of the children in the two studies. It may be, for example, that adolescent children are more susceptible to difficulties associated with parental physical illness than were the younger children assessed in our study. Alternatively, the discrepancy may be due to the different exclusionary criteria used for the medical control groups in the two studies. In our study, medical patients were excluded if they met the criteria for a *DSM-III* diagnosis. In contrast, Hirsch et al. did not assess psychological adjustment in their medical group, and the child adjustment difficulties observed in that study may have been related to undiagnosed psychological problems in the arthritic parents. The importance of assessing psychopathology in medical control subjects is underscored by the results of Hammen et al.'s (10, 11) recent study. As described earlier, these investigators found that medical patients evidenced psychological problems and that the children of these patients demonstrated some adjustment difficulties, although they were not as impaired as the children of depressed parents. Given the small sample of medical patients in our study, our findings may best be considered preliminary pending further empirical validation with a larger sample.

Finally, we should point out that the nondepressed psychiatric patients in our study were rated as less impaired than their depressed counterparts, although both groups scored within the range suggested by Endicott et al. (18) as identifying individuals who require outpatient treatment. It is possible that the group differences in proportions of clinically disturbed children are more a function of the severity of the parents' impairment than they are of the parents' diagnoses. This interpretation would be consistent with findings (26, 27) indicating that severity of maternal impairment has a stronger association with child adjustment than does diagnostic status; clearly, this issue must be addressed more explicitly in future work. Nevertheless, our results do indicate that maternal psychological disturbance is associated with considerable adjustment difficulties in children. Our findings suggest that children's adjustment difficulties may not be specific to parental depressive disorders, and they underscore the need to assess more global aspects of parental psychological disturbance that may adversely affect children's adjustment.

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Life Events of Adolescents in Relation to Personal and Parental Substance Abuse

Sandra A. Brown, Ph.D.

The author examined the life events reported by 138 adolescents in relation to their own and their parents' alcohol and/or drug use. The 62 adolescents who were substance abusers reported more negative events involving deviance and emotional distress and evaluated the life events they experienced as less desirable than did the 76 nonabusing adolescents. Substance-abusing adolescents and the 31 nonabusing adolescents with substance-abusing parents experienced comparable numbers of stressful life experiences; however, the type and qualitative features of the events differed. Adolescents with substance abuse in only one family generation experienced more emotional distress than those with substance use patterns consistent across generations.

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Study of the relationship between life events and adolescent alcohol and/or drug use is relatively new compared with the investigation of the association between psychosocial stress and alcohol and/or drug use among adults. Pandina and Schuele (1) found that higher substance use involvement scores were associated with more negative life events among adolescents. Similarly, Budd et al. (2) reported that among 10,000 Britons 11-17 years old there was a relationship between heavy drinking and financial, academic, and family stress. Few investigations of life events among adolescents have focused on clinical populations of alcohol or drug abusers. Duncan (3) used the Life Event Record for Adolescents (4) to examine life events of drug-dependent adolescents for the year preceding initial illicit drug use. Drug-dependent adolescents acknowledged significantly more stressful life events than

did a group of normal adolescents (3). Unfortunately, comparison of adolescents in treatment with adolescents in school samples is difficult to interpret because these teens may differ in a variety of sociodemographic factors related to incidence of life events.

Life events and alcohol and/or drug use appear to have an iterative and bidirectional relationship. Life events may act as precipitants in the development of abusive drinking or drug use patterns during adolescence. It has been theorized that use of alcohol and drugs may be an attempt to cope with high levels of stressors and life crises during adolescence (3, 5, 6). Conversely, alcohol and drug use during adolescence may also directly or indirectly produce a variety of life problems, including accidents, medical problems, social and familial disruption, job loss, and academic and legal problems.

Psychosocial stress experienced during adolescence may also be influenced by parental alcohol and/or drug abuse. For example, Billings and Moos (7) demonstrated that emotional and health problems are common among the children of alcoholic parents. With parental abstinence for 1 year following alcoholism treatment, however, these children were found to have no higher incidence of either emotional or health problems than children in non-substance-abusing families. Parental alcohol and/or drug abuse may affect the stress that a teen experiences by directly increasing the incidence of stressful events (e.g., marital separation) or by influencing the qualitative features of the life events. For example, parental alcohol abuse cannot be controlled by the adolescent, produces consequences that are difficult to anticipate, and is frequently chronic even following treatment.

The cross-sectional study reported here examined the incidence and subjective evaluations of life events among adolescents in treatment for alcohol and/or drug abuse and a sociodemographically similar group of nonabusing peers. The differences in the stresses experienced by these two groups of adolescents in relation to their parents' alcohol and/or drug use patterns (substance abusing versus nonabusing) were assessed. Three questions were addressed: 1) Is there a higher incidence of life events among adolescents in treatment for substance abuse than among demographically comparable nonabusing peers? 2) Is exposure to substance-abusing parents associated with ele-

Received May 2, 1988; revision received Aug. 30, 1988; accepted Sept. 22, 1988. From the San Diego VA Medical Center and the University of California, San Diego. Address reprint requests to Dr. Brown, Department of Psychiatry (M-003), University of California, San Diego, La Jolla, CA 92093.

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vated levels of undesirable life events or differences in subjective evaluations of events? and 3) Does the type of life events experienced by adolescents vary with personal and parental substance use patterns?

METHOD

Subjects

One hundred thirty-eight 12–18-year-old adolescents participated in the study, which used a 2×2 factorial design of Abusing versus Nonabusing Adolescents by Teens With versus Teens Without Substance-Abusing Parents. Adolescents meeting *DSM-III* criteria for alcohol and/or other drug abuse were selected from treatment programs in the metropolitan San Diego area. Teens fulfilling criteria for other psychiatric disorders (e.g., affective disorder) before the onset of substance abuse and teens who had a history of psychiatric hospitalization were excluded. Of 68 consecutively admitted adolescents who met these criteria and their parents, 62 families (91%) agreed to participate in the study. Thirty-six (58%) of these 62 patients reported no alcohol or drug problems in their parents; 26 (42%) had a parent who abused alcohol and/or drugs identified either by the fact that a parent was participating in an alcoholism-drug abuse treatment program ($N=9$) and/or by parent and teen reports of parent problems sufficient for a *DSM-III* classification of alcohol and/or drug dependence ($N=23$).

Two demographically similar nonabusing groups of adolescents were selected for comparison. Forty-five nonabusing adolescents with substance-abusing parents were recruited from the children of adults in alcohol and drug treatment programs in the hospitals from which the adolescent abusers were drawn. These adolescents met the criteria already described for having a substance-abusing parent. Thirty-one nonabusing adolescents with non-substance-abusing parents were drawn from advertisements at the hospitals and in the surrounding community. Adolescents with a history of alcohol or drug-related problems who met criteria for other *DSM-III* disorders or who had a history of psychiatric hospitalization were excluded from the nonabusing groups.

Most ($N=117$, or 85%) of the 138 adolescents were Caucasian, their mean±SD age was 15.6 ± 2.8 years, and 68 (49%) were male. The occupations of the parents ranged from unemployed laborers to professionals. Eighty-seven (63%) of the 138 parents were married, 33 (24%) were divorced, 10 (7%) were separated, and eight (6%) had never been married. Sixty-one (44%) of the adolescents were Protestants, 35 (25%) were Catholics, 19 (14%) stated they had no religion, and 22 (16%) indicated other religious affiliations. Information on religion was not available for one of the adolescents.

The four groups of adolescents were comparable in

mean±SD school grade (10.2 ± 1.4), parent occupation and socioeconomic status (Hollingshead level= 30.3 ± 7.2), religious and ethnic background, and number of parent previous marriages (1.7 ± 1.4), which was used as a gross indication of general family disruption. However, as reported in other studies of adolescents (8, 9), the nonabusing adolescents participated in religious activities more frequently than did the abusing adolescents ($F=5.92$, $df=3$, 123 , $p<0.01$).

All nonabusers labeled their alcohol consumption pattern as infrequent or moderate, but all teens in treatment defined their drinking as heavy or problematic. A mean Quantity-by-Frequency measure of drinking (ounces of alcohol by days per week) was calculated for the 4 weeks preceding research participation. Adolescent nonabusers had significantly lower Quantity-by-Frequency scores (2.8 ± 2.5) than abusers (14.4 ± 4.1) ($F=58.95$, $df=3$, 129 , $p<0.001$).

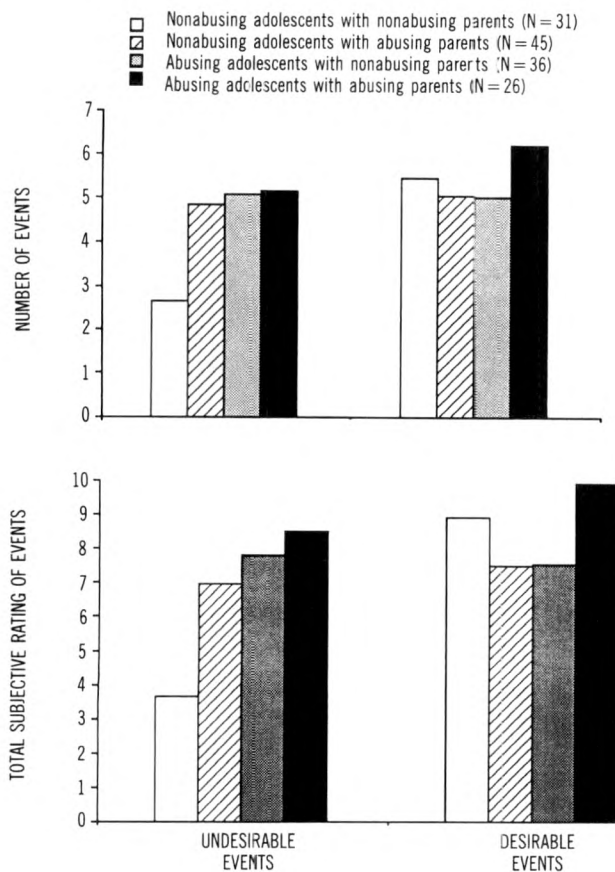
Drug use was prevalent among adolescents in treatment. Marijuana was the most frequently used drug: 56 (90%) of the abusers and five (7%) of the nonabusers reported using marijuana at least four times a week. Cocaine was used by 56 (90%) of abusing adolescents and by 16 (21%) of nonabusers; however, 29 (47%) of the abusers but none of the nonabusers reported regular weekly use of cocaine or crack. There were no significant differences in these drug or alcohol use variables between the nonabusing and abusing adolescent groups based on their parents' substance abuse.

Substance-abusing parents of teens in treatment reported consumption levels and alcohol- and/or drug-related life problems similar to those reported by substance-abusing parents of nonabusing teens. For example, 11 (44%) of the 25 substance-abusing parents of abusing adolescents who answered this question reported blackouts, nine (35%) of 26 reported fighting while drinking, six (23%) of 26 reported multiple alcohol- and/or drug-related arrests, and 18 (72%) of 25 reported multiple failed attempts to stop their abuse. The 45 substance-abusing parents of nonabusing adolescents reported similar problems, but more of them than of substance-abusing parents of abusing adolescents indicated failed attempts at abstinence ($F=21.27$, $df=1$, 70 , $p<0.01$).

Instruments

The 39-item Life Events Checklist developed by Newcomb et al. (10) was used to measure the incidence, subjectively assessed desirability, and type of life events adolescents experienced in the preceding year. The Life Events Checklist is composed of seven mutually exclusive types of life events: 1) family and/or parent problems (e.g., parental separation or divorce and family financial problems), 2) accidents and/or illness (e.g., medical hospitalization), 3) sexuality (e.g., pregnancy, venereal disease), 4) autonomy (e.g., started work, started to drive), 5) deviance (e.g., trouble with the law, school, or employer), 6) relocation

FIGURE 1. Mean Number and Subjective Rating of Life Events in the Preceding Year Reported by 138 Adolescents in Relation to Personal and Parental Substance Abuse



(e.g., family moved, changed schools), and 7) emotional distress (e.g., ran away from home). This instrument was developed in a junior high and high school population ($N=1,018$) and includes items identified in previous research as significant for adolescents (4, 8, 11). Given the lack of consensus regarding measurement of life events (12, 13), both the number of events and the subjective ratings of each event were evaluated. Desirability ratings for events experienced in the preceding year were obtained by using a Likert scale (i.e., very unhappy, unhappy, neutral, happy, very happy).

Procedure

Following independent completion of consent forms, each adolescent and at least one parent completed a separate interview and several questionnaires. (In 10 cases, both parents participated in the interview; data from the first parent interviewed were analyzed.) Teen and parent interviews were conducted by different interviewers to ensure confidentiality, facilitate self-disclosure, and corroborate data. The interview included questions about sociodemographic background, alcohol and/or drug use, psychiatric history

for adolescent and parent abusers, history of alcohol- and/or drug-related problems, and strategies used to cope with pressures associated with drinking and/or drug use. Adolescent and parent substance abusers were interviewed following a minimum of 2 weeks of abstinence. The Life Events Checklist was administered at the end of the teen and parent interviews. The written checklist was given to the participant and then each item was verbally reviewed by the interviewer. For each event, the adolescent indicated whether the event occurred in the preceding year and, if so, his or her subjective evaluation of the impact of this event. Hospitalization for alcoholism and/or drug abuse rehabilitation was not included as a life event. At the conclusion of the interview, each family member was paid \$5.00 for his or her participation. All participation was voluntary and conducted in accordance with the ethical guidelines of the university and treatment programs involved.

RESULTS

The number of desirable and undesirable events and the adolescent's subjective evaluations of events were calculated for each adolescent. The inverse subjective evaluation scores of undesirable events were used so that higher scores meant more negative ratings.

To examine whether adolescent abusers experienced more life events than nonabusing adolescents, the mean number of life events for each group was examined (figure 1). Adolescents in treatment for alcohol and/or drug abuse reported more undesirable life events (5.12 ± 3.18) than did nonabusing teens (3.74 ± 2.39) ($F=10.15$, $df=1, 131$, $p<0.01$). However, this difference primarily reflects the fact that the nonabusing teens with non-substance-abusing parents reported fewer such events (1.63 ± 2.04) than did the other adolescent groups. The nonabusing teens with substance-abusing parents reported as many undesirable events (4.84 ± 2.32) as did the abusing teens. The adolescent groups were similar in their reports of positive life events experienced in the preceding year (overall mean = 5.32 ± 3.06).

A similar pattern of results was evident for the subjective evaluations of life events. As shown in figure 1, the 62 abusing adolescents and the 45 nonabusing teens with substance-abusing parents rated negative events as more undesirable than did the 31 nonabusing teens with non-substance-abusing parents ($F=11.38$, $df=1, 131$, $p<0.01$).

Group scores for desirability of the events were then tested to determine whether having a substance-abusing parent was associated with more stress. The teens with substance-abusing parents rated negative events as significantly more undesirable than did the teens with non-substance-abusing parents ($F=7.09$, $df=1, 131$, $p<0.01$). Additionally, a two-way interaction analysis indicated that the number of undesirable events and subjective evaluations of the desirability of

TABLE 1. Incidence and Type of Life Events in the Preceding Year Reported by 138 Adolescents in Relation to Personal and Parental Substance Abuse

Event Category	Nonabusing Adolescents (N=76)				Abusing Adolescents (N=62)			
	Nonabusing Parents (N=31)		Abusing Parents (N=45)		Nonabusing Parents (N=36)		Abusing Parents (N=26)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Family and/or parent problems ^a	0.74	0.74	2.22	0.83	0.97	0.94	1.01	1.06
Accidents and/or illness	0.83	0.73	1.09	1.02	1.36	1.17	1.23	0.86
Sexuality	1.27	1.09	1.35	1.07	1.59	1.18	1.80	1.23
Autonomy	3.23	1.51	3.42	1.68	2.75	1.75	3.02	1.83
Deviance ^b	0.43	0.76	0.68	0.83	1.50	1.02	1.46	1.14
Relocation	1.08	1.05	0.92	1.01	0.98	0.81	1.12	1.01
Emotional distress ^c	0.99	1.06	1.58	1.04	2.89	1.63	2.53	1.79

^aSignificant adolescent abuse group effect ($F=8.44$, $df=1$, 131, $p<0.01$), parental abuse group effect ($F=25.38$, $df=1$, 131, $p<0.001$), and interaction effect ($F=20.36$, $df=1$, 131, $p<0.001$).

^bSignificant adolescent abuse group effect ($F=32.4$, $df=1$, 131, $p<0.001$).

^cSignificant adolescent abuse group effect ($F=32.71$, $df=1$, 131, $p<0.001$) and interaction effect ($F=4.03$, $df=1$, 131, $p<0.05$).

events varied as a function of both teen abuse ($F=4.03$, $df=1$, 131, $p<0.05$) and parental abuse ($F=4.52$, $df=1$, 131, $p<0.05$). In both cases, nonabusing teens with substance-abusing parents had scores comparable to those of abusing teens in treatment. Thus, in general, abusing teens reported more negative life events and rated those stressful experiences as more undesirable than nonabusing teens. However, nonabusing teens with substance-abusing parents had scores in both domains that were as high as those of abusing teens.

Type of Life Events

To assess whether the type of stressful life experience varied with adolescent or parental substance abuse, the incidence of the seven types of events was examined. Table 1 presents the incidence of each of the seven types of events for the adolescent groups. The most common life events reported by the teens in the present study involved autonomy (3.14 ± 1.68) and emotional distress (2.00 ± 1.57).

A two-way multivariate analysis of variance (MANOVA) was used to determine whether teen groups statistically differed in the incidence of the types of life events that they experienced in the preceding year. The type of stress varied both as a function of teen substance abuse (approximate $F=5.89$, $df=1$, 120, $p<0.001$) and parental substance abuse (approximate $F=2.93$, $df=1$, 120, $p<0.001$) and their interaction (approximate $F=3.61$, $df=1$, 120, $p<0.001$). Specifically, adolescent abusers reported more emotional distress, deviance, and family and/or parent problems (table 1).

Adolescents with substance-abusing parents experienced significantly more parent and/or family problems than did adolescents with non-substance-abusing parents, and nonabusing adolescents with substance-abusing parents reported the highest incidence of family problems (table 1). Of particular interest is the finding that adolescents in families with only one generation of abuse (the nonabusing adolescents with sub-

stance-abusing parents and the abusing adolescents with non-substance-abusing parents) reported a greater incidence of emotional distress events than did abusing adolescents with substance-abusing parents and nonabusing peers with non-substance-abusing parents (table 1).

DISCUSSION

There are three major findings from the present study. First, adolescent substance abuse was associated with a higher incidence of stressful life events. Previous research (1, 2) reported an association between stressful life experiences and adolescent alcohol and/or drug use, and the present study corroborates this association in sociodemographically matched groups of abusing and nonabusing adolescents. Adolescent abusers reported more undesirable life events and rated these events more negatively than nonabusing teens. With the exception of relocation and autonomy events, adolescent abusers tended to report more life events in all categories than nonabusing teens. Autonomy events were the most frequently reported stressors; emotional distress events were as frequent as autonomy events among adolescents in treatment.

The second major finding is that adolescents with substance-abusing parents experienced more stress than teens from non-substance-abusing families. The teens with substance-abusing parents reported more negative life events and rated these events as more undesirable. Further, parent and/or family problems were most prevalent among nonabusing teens with substance-abusing parents, even though all teen groups were comparable on one dimension of family disruption (number of parent marriages).

Adolescents from families with alcohol and/or drug abuse in only one generation (parent or adolescent) reported greater emotional distress than those from families where both generations had similar substance use patterns. Therefore, families with alcohol or drug abuse in only one generation may be more psycholog-

ically distressed by the abuse. Nonabusing teens with abusing parents and abusing teens with nonabusing parents evaluated the desirability of events less positively and obtained higher emotional distress scores. Even in event categories where teens reported equal numbers of events (e.g., autonomy), teens with abuse in one generation of the family evaluated these events less positively than did nonabusing teens with non-substance-abusing parents and abusing teens with substance-abusing parents.

Even though the abusing teens and the nonabusing teens with substance-abusing parents experienced comparable levels of life stress, there appear to be important differences in the qualitative features of their stressors. Specifically, a larger portion of stress in nonabusing adolescents with substance-abusing parents may be independent of teen functioning (e.g., parental separation), more chronic (e.g., family financial problems), and less controllable (e.g., parent accidents or illness secondary to substance abuse). By contrast, stress experienced by abusing teens may be, at least in part, a concomitant or consequence of their own addictive behavior. Given recent evidence that qualitative features of stress such as control (14) and chronicity (15) are important moderators of the impact of stress, children of alcohol and/or drug abusers may be exposed to stress that produces worse negative consequences and may be more vulnerable to the development of stress-related disorders than are their peers.

Adolescent abusers reported twice as many distress experiences and three times as many events involving deviant behaviors as did their nonabusing peers. The associations between substance abuse, deviant behavior, and emotional distress are not new, but they are complex. For example, subtypes of adult alcohol and drug abusers have been identified on the basis of antisocial behavior, depression, and anxiety (16–18), and the chronology of deviant behavior, depression, and alcohol problems appears to have important implications for the clinical course of adult alcohol and drug abusers. Schuckit (19) has demonstrated that alcoholic men meeting criteria for antisocial personality disorder before the onset of alcohol dependence have poorer outcomes following substance abuse treatment. Additionally, alcohol and a variety of other drugs can cause emotional distress, including anxiety, depression, and panic attacks (20, 21).

The present study used a retrospective self-report procedure with interviewer prompting and corroborative parental reports. Therefore, it is limited by the problems inherent to this design and methodology. The cross-sectional design prohibits causal conclusions, and little empirical evidence is available on the reliability of life event reports among adolescents. The fact that the life event assessment was designed to facilitate recall following an extensive interview may have resulted in a greater reporting of life events than use of self-report questionnaires would have. Life event scores of nonabusers were higher than have been

reported in the general adolescent population (10); however, the present sample was specifically selected to match abusing teens demographically. Further, adolescent groups may have differed in their willingness to report life events. Teens in treatment may have attempted to justify their alcohol and/or drug use by attending to stressful experiences or may have been more willing to disclose their experiences as a result of treatment. Alternatively, there may be differential recall of life events among adolescent abusers who have recently been detoxified: potential memory deficits may result in reports that underestimate the actual incidence of events. It should be noted that life event assessment was completed after at least 2 weeks of abstinence from alcohol and drugs in an effort to minimize potential event recall problems. Additionally, the hospitalization for treatment of drug and/or alcohol abuse was not considered an event for adolescents or parents.

One of the strengths and difficulties of the present study is that clinical samples of adolescent abusers and teens with substance-abusing parents in treatment were used. These treatment samples of abusing teens may be different from and in some cases more severe than teens who abuse alcohol or other drugs but are not in treatment. Therefore, findings of the present study may not be generalizable to the general adolescent or adult substance-abusing population and may reflect factors associated with hospitalization rather than specific relationships to alcohol abuse (22). Further comparison of life events across different clinical samples is needed to determine whether higher rates of certain life events are specific to alcohol and drug abuse.

Investigators of psychosocial stress have begun to address the iterative nature of the relationship between life events and health behavior. Not only may life events precede alcohol or drug abuse (3), but the abuse may trigger events such as problems with the law and problems at school, may reduce social resources that buffer the impact of the events, or may compromise one's ability to cope effectively with events (23). This issue becomes more difficult to sort out as the abuse escalates or becomes chronic. Clearly, longitudinal studies with adolescent samples are needed to clarify the temporal relation of life events and abuse and to ascertain the degree of independence or overlap of life events that occurs during and after periods of alcohol and/or drug use.

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Childhood Trauma in Borderline Personality Disorder

Judith Lewis Herman, M.D., J. Christopher Perry, M.P.H., M.D.,
and Bessel A. van der Kolk, M.D.

Subjects with borderline personality disorder (N=21) or borderline traits (N=11) and nonborderline subjects with closely related diagnoses (N=23) were interviewed in depth regarding experiences of major childhood trauma. Significantly more borderline subjects (81%) gave histories of such trauma, including physical abuse (71%), sexual abuse (68%), and witnessing serious domestic violence (62%); abuse histories were less common in those with borderline traits and least common in the subjects with no borderline diagnosis. These results demonstrate a strong association between a diagnosis of borderline personality disorder and a history of abuse in childhood.

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In the past two decades, borderline personality disorder has become the subject of intensive theoretical and clinical investigation. Beginning with Stern (1), successive investigators have refined their descriptive formulations, culminating in the development of *DSM-III* criteria for a reliably identifiable syndrome, stable over time, with serious morbidity (2-9). It is generally agreed that patients with borderline personality disorder are difficult to treat because of the intensity of their engagement with caregivers, the sometimes overwhelming nature of their demands for care, and the strong emotions and conflicts that they provoke in others (10, 11).

Attempts to conceptualize the underlying pathology of borderline personality disorder have generally invoked either a biologic model of affective disorder (12-15) or a psychodynamic model of developmental arrest (10, 11, 16). In the developmental formulation, disruptions in relations with primary caretakers are thought to be an important factor in the genesis of the disorder. Parental neglect and unprotectiveness are

cited by Walsh (17), Frank and Paris (18), Gunderson (6), and Feldman and Guttman (19). Early, prolonged separation from or permanent loss of primary caretakers is described anecdotally by Adler (11) and demonstrated in a significant proportion of patients in retrospective studies by Akiskal (13), Soloff and Millward (15), and Bradley (20).

Although disruption of early attachments is frequently cited, the role of childhood trauma, including parental abuse, in the development of this disorder has received less systematic attention. Data from three small clinical studies offer suggestive evidence that histories of childhood abuse may be especially common in borderline patients. A study of 12 hospitalized borderline patients reported by Stone (21) indicated that 75% had a history of incest. In a chart review study of psychiatric outpatients at an urban teaching hospital, Herman (22) found that eight (67%) of 12 patients diagnosed as borderline according to *DSM-III* criteria had a history of abuse in childhood or adolescence; such histories were found in only 22% of the entire outpatient population. Bryer et al. (23), in an interview study, found that 12 (86%) of 14 hospitalized borderline patients diagnosed by *DSM-III* criteria had a history of sexual abuse before age 16, whereas early sexual abuse was reported by 21% of the entire inpatient population. Although all of these studies involve small numbers of patients, their findings are consistent and provide sufficient evidence to warrant further investigation.

The present study was undertaken to test the hypothesis that a history of childhood trauma is particularly common among patients with borderline personality disorder. A fuller exposition of this hypothesis has been published (24).

METHOD

Subjects were drawn from an ongoing longitudinal study of borderline personality disorder in comparison to the closely related diagnoses of schizotypal personality disorder, antisocial personality disorder, and bipolar II affective disorder. Subjects were originally recruited from ambulatory mental health settings and from advertisements for symptomatic volunteers. The methods of subject selection have been previously described in detail (9, 25, 26). After full explanation of

Received March 28, 1988; revision received Sept. 22, 1988; accepted Oct. 18, 1988. From the Department of Psychiatry, Harvard Medical School, The Cambridge Hospital, Cambridge, Mass. Address reprint requests to Dr. Herman, 61 Roseland St, Somerville, MA 02143.

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the study, informed consent was obtained from all subjects, who were paid for their time at each interview.

Most diagnostic interviews were conducted by the principal investigator of the longitudinal study (J.C.P.). Definite borderline personality disorder was diagnosed if the subject met the cutoff of five or more *DSM-III* criteria and had a score higher than 150 on the Borderline Personality Scale, second version, a 52-item precursor of the Borderline Personality Disorder Scale, that rates major features of the disorder in nine subcategories (25, 26). Borderline trait was diagnosed if the subject met at least four *DSM-III* criteria and had a score higher than 130 on the Borderline Personality Scale. Antisocial and schizotypal personality disorders were diagnosed according to *DSM-III* criteria. Bipolar II disorder was diagnosed according to Research Diagnostic Criteria (27).

Childhood histories were obtained by means of a 100-item semistructured interview, which generally required 2 hours (Herman and van der Kolk, unpublished manuscript). The interview covered a description of primary caretakers and other important relationships in childhood and adolescence, major separations, moves and losses, sibling and peer relationships, family discipline and conflict resolution, family alcoholism, domestic violence, and physical and sexual abuse. Subjects were encouraged to narrate their experiences in detail, rather than simply providing yes or no answers to questions, so that the internal consistency and credibility of the history could be evaluated. All interviews were conducted by one of the authors (J.H. or B.vdK.). Interviewers were blind to the subjects' diagnoses and all other previously obtained information.

The interviews were scored for positive indexes of trauma in three areas: physical abuse, sexual abuse, and witnessing domestic violence. Instances of culturally-accepted corporal punishment and fighting or consensual sexual exploration between peers were not rated as abusive. Equivocal situations were scored as negative.

Protocols were scored for occurrence of each type of trauma at each of three developmental stages: early childhood (0–6 years), latency (7–12 years), and adolescence (13–18 years). Within each developmental stage, no distinction in scoring was made between single and repeated instances of abuse by the same perpetrator; however, additional positive scores in each category were given for abuse by different perpetrators. A rough composite measure of trauma was constructed by adding the positive scores for each category of trauma at each developmental stage. Thus a range of scores was generated from 0 (no trauma at any developmental stage) to 9 or higher (all three forms of trauma at all three stages or multiple perpetrators at one or more stages).

In addition to the structured interview, subjects completed two brief self-report questionnaires: the Impact of Event Scale (28), which was used as a measure of current symptoms of posttraumatic stress disorder,

and the Dissociative Experiences Scale (29), which probed familiarity with dissociative states.

Data analysis was conducted by means of cross-tabulation and Kendall's tau computation for ordinal by categorical tables. General linear models procedure for analysis of variance (ANOVA) with post hoc analysis for comparison of means was used for continuous variables. Spearman correlation coefficients were calculated for bivariate relationships.

RESULTS

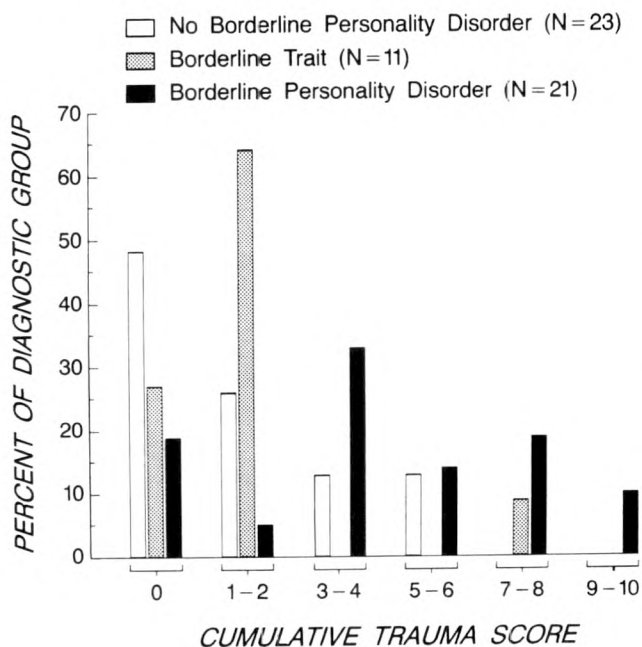
Of 75 subjects enrolled in the ongoing longitudinal study, we were able to contact 58 (77%) during the time period in which this investigation was conducted (June 1986 to December 1987). Three subjects refused to participate after being informed of the content of the interview. Of the 55 subjects, 29 women and 26 men, who participated in the trauma interviews, 21 (17 women and four men) were diagnosed as having definite borderline personality disorder, 11 (all men) as having borderline traits, 11 (six women and five men) as having bipolar II disorder, six (three women and three men) as having antisocial personality disorder, and six (three women and three men) as having schizotypal personality disorder.

The frequencies of abuse histories in each diagnostic category are given in table 1. The great majority ($N=17$ or 81%) of subjects with definite borderline personality disorder gave histories of major childhood trauma; 71% ($N=15$) had been physically abused, 67% ($N=14$) had been sexually abused, and 62% ($N=13$) had witnessed domestic violence. Abuse histories were less common in patients with borderline trait and least common in the subjects with no borderline diagnosis. Histories of trauma in early childhood (0–6 years) were found almost exclusively in borderline subjects, and over half of the borderline subjects ($N=12$ or 57%) reported such experiences in early childhood. Borderline subjects also reported significantly more abuse experiences in latency than other subjects. The differences between the groups diminished with increasing age at onset of abuse, becoming least significant in adolescence.

Borderline subjects not only suffered from abusive experiences more commonly than others but also reported more types of trauma, beginning earlier in childhood and repeated over longer time periods, resulting in higher total trauma scores. The distribution of childhood trauma scores is given in figure 1. Scores ranged from zero (18 subjects) to 10 (one subject). An ANOVA of mean trauma score by borderline diagnosis was significant ($F=7.82$, $df=2$, 54, $p=0.001$), and a post hoc analysis ($\alpha=0.05$) indicated that the mean trauma score for the group with definite borderline personality disorder (4.29 ± 2.89) was significantly higher than the means for the group with borderline traits (1.73 ± 1.95) and the means for those with any nonborderline closely related diagnosis (1.63 ± 2.05).

TABLE 1. Traumatic Childhood Experiences in 55 Subjects in Longitudinal Study of Borderline Personality Disorder

Age at Onset and Type of Trauma	Borderline Personality Disorder (N=21)		Borderline Trait (N=11)		No Borderline Personality Disorder (N=23)		Analysis		
	N	%	N	%	N	%	Kendall's tau	Z	p
Early childhood (0–6 years)									
Physical abuse	7	33	0	0	1	4	0.34	3.14	<0.005
Sexual abuse	4	19	1	9	0	0	0.28	3.39	<0.001
Witness to domestic violence	7	33	0	0	2	9	0.28	2.20	<0.05
Any trauma	12	57	1	9	3	13	0.40	3.48	<0.001
Latency (7–12 years)									
Physical abuse	15	71	2	18	5	22	0.42	3.63	<0.001
Sexual abuse	7	33	2	18	2	9	0.26	2.22	<0.05
Witness to domestic violence	10	48	4	37	5	22	0.23	1.87	<0.10
Any trauma	17	81	6	55	8	35	0.39	3.49	<0.001
Adolescence (13–18 years)									
Physical abuse	13	62	3	27	8	35	0.23	1.79	<0.10
Sexual abuse	11	52	2	18	6	26	0.23	1.80	<0.10
Witness to domestic violence	10	48	2	18	5	22	0.23	1.83	<0.10
Any trauma	17	81	5	45	12	52	0.25	2.07	<0.05
All ages (0–18 years)									
Physical abuse	15	71	4	36	9	39	0.27	2.20	<0.05
Sexual abuse	14	67	3	27	6	26	0.34	2.87	<0.005
Witness to domestic violence	13	62	4	36	7	30	0.27	2.16	<0.05
Any trauma	17	81	8	73	12	52	0.31	2.67	<0.01

FIGURE 1. Distribution of Childhood Trauma Scores Among 55 Subjects in a Longitudinal Study of Borderline Personality Disorder

Rating total childhood trauma as a continuous variable allowed for correlation with degree of personality pathology, as measured by the Borderline Personality Disorder Scale, antisocial personality disorder lifetime symptom count, and schizotypal personality disorder lifetime symptom count (table 2). Degree of borderline psychopathology was positively correlated with all three forms of childhood trauma. No such correlation

TABLE 2. Correlations Between Personality Disorder Measures and Childhood Trauma Scores of 55 Subjects in a Longitudinal Study of Borderline Personality Disorder

Type of Childhood Trauma	Spearman Correlation (r_s)		
	Schizotypal	Antisocial	Borderline
Physical abuse	0.03	0.15	0.47 ^a
Sexual abuse	0.11	0.12	0.40 ^b
Witness to domestic violence	-0.07	0.12	0.40 ^b
Total	0.03	0.22	0.53 ^a

^a $p < 0.001$.

^b $p < 0.01$.

was found for antisocial or schizotypal personality pathology, although a trend relationship was found between antisocial symptom count and total trauma score ($p < 0.10$).

As anticipated, gender differences were also significant. The mean total trauma score was 3.64 ± 2.97 for women and 1.58 ± 1.81 for men ($\alpha = 0.05$). Women reported more physical and more sexual abuse in childhood, whereas witnessing domestic violence was reported equally by men and women. After controlling for diagnosis, the gender difference disappeared with respect to reports of physical abuse ($F = 0.28$) but remained significant with respect to reports of sexual abuse ($F = 8.74$, $df = 4, 50$, $p = 0.005$). The positive association between a borderline diagnosis and total childhood trauma score remained significant when the effects of gender differences were controlled. An ANOVA showed main effects for gender ($F = 10.46$, $df = 4, 50$, $p = 0.002$) and diagnosis ($F = 4.51$, $df = 4, 50$, $p = 0.016$) and no significant interaction effect between gender and diagnosis ($F = 0.02$).

After controlling for diagnosis, the gender effect diminished to a significant trend ($F=3.28$, $df=4$, 50 , $p=0.08$). After gender was controlled for, the effect of diagnosis remained significant ($F=3.71$, $df=4$, 50 , $p=0.03$).

The subjects with personality disorders generally reported high levels of dissociative symptoms. Bivariate analyses with scores on the Dissociative Experiences Scale demonstrated a significant correlation with scores on the Borderline Personality Disorder Scale ($r_s=0.29$, $N=55$, $p=0.03$) and a trend correlation with lifetime schizotypal symptoms ($r_s=0.26$, $N=55$, $p=0.06$) but no correlation with lifetime antisocial symptoms ($r_s=0.19$). Hierarchical regressions were conducted to predict the Dissociative Experiences Scale score on the basis of the Borderline Personality Disorder Scale and the total childhood trauma scores. The scores on the Borderline Personality Disorder Scale were significant when entered first ($F=4.83$, $df=2$, 52 , $p=0.03$) but not significant when the childhood trauma scores were entered first ($F=.34$); however, the total childhood trauma score was significant even when entered second ($F=5.42$, $df=2$, 52 , $p=0.02$). No differences were found between borderline, borderline trait, and nonborderline subjects with respect to post-traumatic symptoms as measured by the Impact of Event Scale ($F=0.27$).

DISCUSSION

These results demonstrate a strong association between borderline personality disorder and a reported history of childhood abuse. The great majority of borderline subjects reported such a history. Although abuse experiences were also reported by some subjects with closely related diagnoses, they were less common and cumulatively less severe. Early childhood histories of abuse and multiple childhood abuse experiences as reflected by very high trauma scores were found almost exclusively among borderline subjects.

The importance of our findings is enhanced by the conservative definitions that were used in scoring trauma histories as positive. We found no evidence to suggest that such histories were exaggerated or fabricated. The following case examples, disguised for protection of subjects' identities, illustrate the contrasting types of histories reported by our subjects and the judgments that were made in assigning trauma scores.

Case 1. Ms. A, a 35-year-old woman with borderline personality disorder, was the fourth of five siblings born to two alcoholic parents. After her father deserted the family when she was 3 years old, the household became increasingly chaotic; her mother enforced unclear and inconsistent rules by screaming, hair pulling, hitting on the head and face, and kicking in the knees and genital area. In Ms. A's words, "You never knew when to expect it. You could do something really wrong and she wouldn't notice, and then you could knock over your milk and she would fly off the handle." Her mother remarried when Ms. A was 9 years old, and the level

of violence in the home diminished. Shortly after entering the home, however, the stepfather began sexually molesting Ms. A and her three sisters. The incestuous relationship, which proceeded to oral sex and intercourse, continued until she ran away from home at age 15. While on the road, Ms. A frequented bars where she would pick up older men, offering sex in exchange for shelter. At age 17 she was brutally raped and beaten in one such encounter, requiring hospitalization for her injuries. Ms. A received a trauma score of 5 (physical abuse in early childhood and latency, sexual abuse in latency and adolescence, and rape in adolescence).

Case 2. Mr. B, a 28-year-old man with borderline traits, described an intact family with a capricious and domineering father and a compliant, submissive mother. He described very restrictive family rules, "like boot camp," and frequent corporal punishment (hitting with a belt) and stated that "If my father had been left to his own devices, I would have been a battered child, but my mother protected me." He described one incident at age 11 in which his father became enraged, chased him into his room screaming "I'll kill you," cornered him, and began to strangle him. His mother attempted to intercede, at which point his father attacked her, struck her in the face with a closed fist, and knocked her to the ground. After this attack, his father was remorseful, and no similar incidents occurred. Mr. B received a trauma score of 2 (one incident each of physical abuse and witnessing domestic violence).

Case 3. Ms. C, a 38-year-old woman with bipolar II disorder, was the youngest daughter among eight children. Her father was a severe alcoholic, and she described her mother as raising the family single handedly. She described her mother's discipline as very strict: "She was very old country; she was trying to cope too." Although discipline was carried out by means of frequent hitting with a cane or a "bony Irish hand," Ms. C stated that "It was not traumatic, she did it with everybody, it seemed all right; the nuns at school did it too." When Ms. C was 10 years old, her 14-year-old brother began to involve her in sexual games, including showing and fondling of genitals, kissing, and imitation of activities shown in pornographic magazines. She idealized her brother, was grateful for the attention, and in spite of the age difference did not perceive the sexual relationship as exploitative until she was 12 years old, at which time her brother attempted to bribe her to perform the same activities with his friends. She felt deeply betrayed and angrily refused. Ms. C received a trauma score of 0 (harsh but nonabusive corporal punishment, equivocal sexual abuse).

Although no definitive conclusions regarding the etiology of borderline personality disorder can be drawn from correlations based on retrospective data, the hypothesis that childhood abuse has a major formative role in the development of the disorder is strongly supported by our findings. The strength of the association between childhood trauma and borderline personality disorder suggests that it is an important factor but not alone sufficient to account for borderline psychopathology. It is possible that trauma is most pathogenic for children with vulnerable temperaments or for those most lacking protective factors, such as positive relationships with other caretakers or siblings.

Despite severe abuse histories, the borderline sub-

jects did not report current symptoms of posttraumatic stress disorder, at least as measured by the Impact of Event Scale. It appeared that memories of the abuse had become integrated into the total personality organization and had become essentially ego syntonic. The subjects generally did not perceive a direct connection between their current symptoms and abusive experiences in childhood. This finding is compatible with observations from follow-up studies of trauma victims (30, 31) which indicate that fragments of the trauma may be transformed over time and relived in a variety of disguised forms, e.g., as somatic sensations, affect states, visual images, behavioral reenactments, or even dissociated personality fragments. Our finding that dissociative symptoms were more strongly correlated with childhood trauma than with borderline psychopathology per se is consistent with the recent finding of Spiegel et al. (32) that dissociation and trauma are highly correlated.

Childhood trauma has been implicated as an etiological factor in such diverse psychiatric conditions as somatoform disorder (33), panic disorder (34), and multiple personality disorder (35–38). Thus, it might be possible to conceptualize a range of adaptations to childhood trauma, or trauma spectrum disorders, with multiple personality disorder representing an extreme adaptation to severe chronic abuse, borderline personality disorder representing an intermediate form of adaptation to chronic abuse, and some forms of somatoform, panic, and anxiety disorders representing dissociated somatic reexperiencing of more circumscribed traumatic events (30).

Childhood abuse as an important antecedent to the development of borderline personality disorder could explain in part the higher prevalence of borderline personality disorder in women. Epidemiologic data on child abuse (39) indicate that although boys and girls are at approximately equal risk for physical abuse, girls are at two to three times greater risk for sexual victimization. Moreover, sexual abuse is apparently more prevalent, and often more prolonged, than physical abuse (40). Thus, girls may be more frequently exposed to conditions favoring the development of borderline personality disorder.

Conceptualizing borderline personality disorder as a complicated posttraumatic syndrome has direct implications for the treatment of patients. Clinical literature on the treatment of posttraumatic syndromes (41–48) has shown the importance of recovery and integration of traumatic memories with their associated affects and the necessity for validation of the patient's traumatic experiences. The integration of the trauma is a precondition for development of improved affect tolerance, impulse control, and defensive organization; the validation of the trauma is a precondition for restoration of an integrated self-identity and the capacity for appropriate relationships with others. Posttraumatic states are often undiagnosed in cases in which secrecy or stigma prevents recognition of the traumatic origins of the disorder; such patients may show re-

markable improvement when the connection between symptom and trauma is recognized. Whether some of the negative therapeutic reactions so frequently observed in borderline patients might be avoided by early and appropriate recognition of the relationship between the patient's current symptoms and traumatic experiences in childhood remains to be determined.

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Personality Disorder in the Families of Depressed, Schizophrenic, and Never-Ill Probands

William H. Coryell, M.D., and Mark Zimmerman, B.A.

In a blind family study of 176 probands with non-psychotic major depression, psychotic major depression, schizophrenia, or no history of DSM-III disorders, only the relatives of depressed probands with mood-incongruent psychotic features had a risk for personality disorders higher than that for the relatives of never-ill probands. The authors did not find a high rate of borderline personality in relatives of depressed probands or of schizotypal personality disorder in relatives of probands with schizophrenia or any psychosis. However, depressed probands with normal dexamethasone test results had a significantly higher familial loading for the DSM-III cluster of histrionic, antisocial, borderline, and narcissistic personality disorders.

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The descriptions of most *DSM-III* personality disorders represent simply the clinical experience of interested clinicians; only a few—antisocial personality, borderline personality disorder, and schizotypal personality disorder—have been the targets of widespread empirical research. Diverse approaches have been taken to study antisocial personality, but most of the work on schizotypal and borderline personality disorders has emphasized phenomenology and familial patterns of psychopathology. These studies have not been limited in their implications, however. They have gone beyond simply supporting the validity of these categories and have linked them to other discrete disorders. These findings invite an extension of such approaches to other personality disorders.

Family studies (1-4) have shown not only high rates of borderline personality disorder among the relatives of borderline probands but also high rates of major depression. Together with the results of follow-up (5-7) and neuroendocrine (8, 9) studies, these findings strongly suggest a link between borderline personality

disorder and affective disorder. Such a link may involve only subsets of one or both disorders. For instance, the relatives of probands with bipolar affective disorder apparently are not at higher risk for borderline personality than are the relatives of schizophrenic probands (2, 3). Does the borderline-affective disorder spectrum involve only nonbipolar conditions, and, if so, are only certain nonbipolar conditions relevant? Finally, only one of these studies (3) employed a family study design, and, even here, only one-half of the relatives were directly interviewed. Did these studies lack sufficient sensitivity to detect a clustering of borderline personality disorder among relatives of affectively ill probands?

Schizotypal personality disorder appears more often in the families of schizophrenic probands than in the families of control probands (10-12), although the reverse apparently does not hold (11, 13). Moreover, the relatives of schizotypal probands have a higher than normal risk for schizotypal personality disorder (1, 14). Whether this disorder is specific to the families of schizophrenic probands or is also prevalent in the families of other psychotic probands is unknown, however. It is possible that schizotypal personality disorder is associated with a psychotic diathesis rather than with schizophrenia per se.

Other *DSM-III* personality disorders may also be linked to affective disorders, to schizophrenia, or to psychosis in general; the relevant existing data are limited. Family studies have suggested connections between antisocial personality disorder and certain depressive disorders (15) and between paranoid personality disorders and schizophrenia (16). Still other personality disorders may fall on a spectrum with affective illness or schizophrenia, as might clusters of personality disorders. Indeed, comorbidity among the personality disorders is the rule (17, 18) and appropriate grouping may increase the likelihood of identifying familial relationships between axis I and axis II disorders.

Finally, certain individual disorders or clusters may be associated not with affective disorder in general but with a particular subtype. Recent efforts to define neurotic depression (19, 20) have emphasized the importance of a chaotic lifestyle. Such lifestyles are inherent in the "acting out" personality disorders (the second *DSM-III* cluster—histrionic, narcissistic, antisocial, and borderline personality disorders). Perhaps a pre-

Received Feb. 29, 1988; revision received Sept. 22, 1988; accepted Oct. 18, 1988. From the Department of Psychiatry, University of Iowa College of Medicine. Address reprint requests to Dr. Coryell, Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

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disposition both to these personality disorders and to neurotic or nonmelancholic depression clusters within families. Unfortunately, this subtype of depression has persistently eluded any definition that is both operational and widely accepted. This situation necessitates the simultaneous use of different definitions.

The family study we will describe involved probands with the major functional psychoses or nonpsychotic major depression and probands who had never been psychiatrically ill. The probands with major depression were further subdivided on the basis of presence or absence of melancholia and dexamethasone suppression test (DST) results. The presence or absence of each *DSM-III* personality disorder was determined in all available first-degree relatives. Given these resources, we undertook the following analyses first to simply explore a wide range of possible familial relationships between axis II disorders (or clusters thereof) and axis I disorders. Previous research suggested that 1) there would be a high prevalence of borderline personality disorder in the relatives of the depressed probands, 2) there would be a high prevalence of schizotypal personality disorder among the relatives of the schizophrenic probands, or at least the relatives of the psychotic probands, and 3) the "acting out" axis II disorders would cluster in the families of probands with nonendogenous depression, variously defined.

METHOD

The proband evaluations took place in two sequential studies. In the first (21), all patients admitted to the University of Iowa Psychiatric Hospital with nonmanic functional psychoses were included in the study if they consented, were over 17 years of age, and lacked medical or pharmacological conditions that would have invalidated either the results of the DST or the thyroid-releasing-hormone stimulation test. The resulting sample consisted of all consecutively admitted patients who met these criteria; the investigators did not eliminate diagnostically confusing cases.

One of us (M.Z.) used full record review and direct patient interviews to complete a Schedule for Affective Disorders and Schizophrenia (SADS) (22) for each proband and to assign a diagnosis according to each of several systems, including *DSM-III*. The other one of us (W.C.) conducted an independent, unstructured interview and likewise determined diagnoses. We then met to reach a consensus in each case. Follow-up data clearly documented the success of this enterprise—patients with major depression and mood-congruent psychotic features were 12 times as likely to have recovered at 6 months as were patients with schizophrenia (23).

In the meantime, research assistants who were blind to proband diagnoses contacted all first-degree relatives who were 17 years of age or older. Geographic location did not determine inclusion, as most interviews (574, or 73%) were by phone. The interviewers

used the highly structured Diagnostic Interview Schedule (DIS) (24) to determine axis I diagnoses and the Structured Interview for *DSM-III* Personality Disorders (25, 26) to determine personality disorders. The latter contains 160 questions in 16 labeled sections, e.g., "self-esteem," "perception of threat." Corresponding *DSM-III* items follow each section and can be rated 0, 1, or 2. We have consistently used a rating of either 1 or 2 to indicate symptom presence. In contrast to an earlier study (18), however, in this study we used all the exclusion criteria specified by *DSM-III*.

Our analyses also included the personality disorder clustering suggested by *DSM-III*. The first cluster—paranoid, schizoid, and schizotypal personality disorders—applies to individuals who are "odd" or eccentric." Histrionic, narcissistic, antisocial, and borderline personality disorders constitute the second—"dramatic, emotional, or erratic"—cluster, and avoidant, dependent, compulsive, and passive-aggressive personality disorders make up the third, "anxious or fearful," cluster. The subjects given diagnoses of mixed personality disorders were within one criterion of two or more personality disorders and did not meet the criteria for a specific personality disorder.

Both research assistants had participated in other protocols that required structured interviews of psychiatric inpatients. In addition, each had completed a 1-month training program for the Structured Interview for *DSM-III* Personality Disorders and the 1-week intensive DIS program offered in St. Louis. The reliability with which these raters scored the Structured Interview for *DSM-III* Personality Disorders for 104 relatives was assessed with audiotapes and an observer-rater design. The kappa coefficients for the six disorders diagnosed two or more times were all above 0.65 (unpublished data).

A reliance on telephone interviews involved certain disadvantages, which we weighed against the considerable sampling biases introduced by limiting the subjects to those available for personal interviews. In fact, comparisons of the frequencies with which the individual axis I and axis II diagnoses were made revealed no significant differences between the telephone and in-person assessments.

Recruitment of the probands with nonpsychotic major depression and the never-ill control probands began as the family study of nonmanic psychotic probands neared completion. Sequentially admitted patients with nonpsychotic major depression were recruited if they were 17 years or older, regardless of whether they had conditions precluding valid neuroendocrine test results. The proband diagnostic evaluation was identical to that for the preceding series of psychotic patients, as was the evaluation of all available first-degree relatives. This evaluation was conducted blindly as well, since the relatives of never-ill control probands were being interviewed concurrently.

Inpatient subjects received 1 mg of dexamethasone at 11:00 p.m. within a week of admission; plasma samples for cortisol determinations were obtained the

following day at 8:00 a.m., 4:00 p.m., and 11:00 p.m. Treatment was entirely naturalistic and was neither postponed nor interrupted by the study protocol. Cortisol levels were measured by means of radioimmunoassay with a specific cortisol antiserum. There was no cross-reactivity with dexamethasone, progesterone, testosterone, or 11-deoxycortisol. The intra-assay and interassay coefficients of variation were 12.2% and 11.1%, respectively, at concentrations near the cutoff to classify patients as nonsuppressors.

The control sample has been described elsewhere (27). Briefly, the advertisements targeted hospital personnel, and those who responded passed three phases of screening, ending with a SADS-L and a Structured Interview for DSM-III Personality Disorders. Only those with no lifetime history of psychiatric disorders, as defined by the Research Diagnostic Criteria (RDC) (28) and *DSM-III* axis II, were included in the family study.

We used chi-square tests for categorical comparisons and nonparametric, two-tailed *t* tests for comparisons involving continuous measures. The exploratory nature of the analyses required many statistical comparisons, and only a few specific predictions were imbedded within them. To correct the alpha level for the number of tests would have raised the risk of inappropriately failing to sustain certain of these hypotheses. As it happened, the unexpected negative results (no significant difference) far outnumbered the unexpected positive ones.

RESULTS

Of 967 living relatives, 786 (81.3%) were successfully interviewed, and this proportion did not vary significantly by proband axis I diagnosis (table 1). The rate of each personality disorder was low, and only antisocial and schizotypal personality disorders were found in more than 5% of the relatives of any proband group. Both of these disorders were particularly common among the relatives of the depressed probands with mood-incongruent psychotic features, and personality disorder in general seemed overrepresented among these relatives. Six of the 10 personality disorders diagnosed at all were most common in this group, although by chance only two would be expected to predominate in a single group.

The results supported few of the predictions. Specifically, borderline personality disorder was not significantly more common among the relatives of depressed patients (10 of 473, 2.1%) than it was among the relatives of control subjects (1.1%) or schizophrenic patients (0.8%). Likewise, schizotypal personality was not significantly more common in the families of schizophrenic patients (2.3%) or in the families of probands with any psychosis (13 of 373, 3.5%) than in the control subjects' relatives (2.2%). Paranoid personality disorder in relatives was not associated with a proband diagnosis of either schizophrenia or psychosis in general.

The data did support certain other predictions (table 2). Personality disorder diagnoses from cluster 2 were given to nearly twice as many relatives of nonmelancholic probands as relatives of their melancholic counterparts. Similarly, significantly more of the relatives of DST suppressors were given cluster 2 diagnoses than either relatives of DST nonsuppressors or relatives of never-ill control probands (4.3%) (relatives of suppressors versus relatives of control probands: $\chi^2=4.2$, *df*=1, *p*<0.05). The difference in prevalence of cluster 2 diagnoses between the relatives of never-ill control probands and the relatives of probands who were both suppressors and nonmelancholic was highly significant ($\chi^2=7.0$, *df*=1, *p*<0.01). On the other hand, the differences were not enhanced by restricting the numerators in the rates to the relatives who had cluster 2 personality disorders only.

An unexpected but relatively robust relationship emerged between proband polarity and cluster 3 personality disorders among relatives (table 3). Two to three times as many relatives of bipolar probands had cluster 3 diagnoses, and this difference remained significant after the relatives with both cluster 3 personality disorders and bipolar (*N*=1) or atypical bipolar (*N*=1) disorder were excluded. Compulsive, passive-aggressive, and dependent personality disorders (but not avoidant personality disorder) were each diagnosed in more relatives of bipolar probands, although none of the comparisons for individual personality disorders reached statistical significance.

Personality disorders in general did not cluster within pedigrees. Overall, 17.9% (141 of 786) of the interviewed relatives each had at least one personality disorder, and these relatives were distributed across 87 pedigrees. When one affected relative was removed from each pedigree, only 16.0% of the remaining relatives had at least one personality disorder each. Thus, the presence of one affected relative did not appear to raise the likelihood that the remaining relatives in a given pedigree would be affected.

DISCUSSION

Contrary to expectations, schizotypal personality disorder appeared to be linked to neither schizophrenia nor psychosis in general. In an earlier analysis (29) we described psychotic and never-ill probands grouped according to the RDC and likewise failed to find a higher rate of schizotypal personality among the relatives of schizophrenic probands. The relevant methodological issues in that study were discussed in some detail. In particular, findings were not substantially changed when we restricted the analysis to relatives interviewed in person. The proportions not interviewed in the present study probably did not produce falsely negative results. Baron et al. (1) adopted a very similar design, interviewed a similar proportion of relatives (83%), and yet found seven times the rate of schizotypal personality disorder in

TABLE 1. *DSM-III* Personality Disorders Among Relatives of Probands With Major Depression, Schizophrenia, or No *DSM-III* Axis I or II Disorder

Variable	Nonpsychotic Major Depression				Major Depression With Psychotic Features								Schizophrenia				No <i>DSM-III</i> Disorder			
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD
Probands	56				24				28				32				36			
Relatives living	293				132				177				159				206			
Relatives interviewed	228	77.8			117	88.6			128	72.3			128	80.5			185	89.8		
Female sex	128	56.1			68	58.1			73	57.0			70	54.7			98	53.0		
Age (years) ^a			42.5	17.1			44.2	16.7			40.6	15.8			42.8	16.3			39.6	16.0
Personality disorders among relatives																				
Cluster 1																				
Paranoid																				
Diagnosis	3	1.3			0	0.0			2	1.6			1	0.8			1	0.5		
Traits			1.1	1.7			1.3	1.7			1.4	1.9			1.2	1.7			1.3	1.5
Schizoid																				
Diagnosis	1	0.4			1	0.9			0	0.0			0	0.0			3	1.6		
Traits			0.2	0.5			0.3	0.6			0.2	0.5			0.2	0.5			0.2	0.6
Schizotypal																				
Diagnosis	6	2.6			3	2.6			7	5.5			3	2.3			4	2.2		
Traits			0.7	1.0			0.8	1.2			0.9	1.3			0.6	0.9			0.6	1.0
Any																				
Diagnosis	10	4.4			4	3.4			8	6.3			4	3.1			7	3.8		
Traits			2.0	2.8			2.4	2.8			2.5	3.1			2.1	2.5			2.1	2.7
Cluster 2																				
Histrionic																				
Diagnosis	11	4.8			3	2.6			4	3.1			3	2.3			3	1.6		
Traits			1.4	1.6			1.2	1.5			1.4	1.6			1.0	1.3			1.2	1.5
Antisocial																				
Diagnosis	7	3.1			1	0.9			9	7.0			5	3.9			3	1.6		
Traits			1.9	2.6			1.3	1.9			2.4	2.9			1.4	2.0			1.4	1.9
Borderline																				
Diagnosis	4	1.8			2	1.7			4	3.1			1	0.8			2	1.1		
Traits			0.6	1.1			0.7	1.1			1.0	1.4			0.6	1.0			0.6	1.0
Narcissistic																				
Diagnosis	0	0.0			0	0.0			0	0.0			0	0.0			0	0.0		
Traits			0.4	0.9			0.4	0.9			0.5	1.1			0.4	0.8			0.5	0.8
Any																				
Diagnosis	17	7.5			6	5.1			12	9.4			9	7.0			8	4.3		
Traits			4.5	5.1			3.7	4.2			5.5	5.6			3.5	4.0			3.7	4.1
Cluster 3																				
Compulsive																				
Diagnosis	5	2.2			1	0.9			2	1.5			2	1.6			6	3.2		
Traits			0.8	1.0			0.8	0.9			0.7	0.9			0.7	0.9			0.8	1.0
Passive-aggressive																				
Diagnosis	4	1.8			4	3.4			5	3.9			1	0.8			4	2.2		
Traits			1.1	1.7			1.1	1.9			1.6	2.2			1.0	1.5			1.1	1.8
Dependent																				
Diagnosis	10	4.4			0	0.0			3	2.3			0	0.0			1	0.5		
Traits			0.4	0.8			0.2	0.5			0.3	0.6			0.2	0.6			0.2	0.4
Avoidant																				
Diagnosis	0	0.0			2	1.7			5	3.9			0	0.0			3	1.6		
Traits			0.6	1.0			0.7	1.2			0.8	1.4			0.5	0.9			0.5	0.9
Any																				
Diagnosis	19	8.3			6	5.1			15	11.7			3	2.3			13	7.0		
Traits			4.8	2.8			4.5	3.3			5.2	3.8			4.3	2.5			4.3	2.7
Mixed disorders	9	3.8			6	5.1			6	4.7			4	3.1			4	2.2		
Any axis II disorder																				
Diagnosis	45	19.7			20	17.1			32	25.0 ^b			17	13.3			27	14.6		
Traits			10.3	9.0			9.8	8.8			12.0	10.8			9.1	7.2			9.2	7.8

^aThe age ranges of the groups were as follows: nonpsychotic major depression, 17–82 years; major depression with mood-congruent psychotic features, 18–91 years; major depression with mood-incongruent psychotic features, 17–79 years; schizophrenia, 18–84 years; no axis I or II disorder, 16–89 years.

^bSignificantly different from relatives of probands with no disorders ($\chi^2=5.0$, $df=1$, $p<0.025$).

TABLE 2. DSM-III Personality Disorders Among Relatives of Probands With Major Depression Grouped by Melancholia and Suppression on DST

Variable	Melancholia				Suppression on DST				Melancholia and Nonsuppression			
	Yes		No		No		Yes		Both		Neither	
	N	%	N	%	N	%	N	%	N	%	N	%
Probands	28		79		42		44		11		32	
Relatives interviewed	129		344		181		207		42		148	
Relatives with personality disorders												
Cluster 1												
Paranoid	1	0.8	4	1.2	1	0.6	2	1.0	1	2.4	2	1.4
Schizoid	0	0.0	2	0.6	0	0.0	2	0.5	0	0.0	1	0.7
Schizotypal	4	3.1	12	3.5	6	3.3	8	3.9	2	4.8	7	4.7
Any	4	3.1	18	5.2	7	3.9	11	5.3	2	4.8	10	6.8
Cluster 2												
Histrionic	3	2.3	15	4.4	4	2.2	10	4.8	0	0.0	8	5.4
Antisocial	2	1.6	15	4.4	2	1.1	10	4.8	0	0.0	10	6.8
Borderline	1	0.8	9	2.6	3	1.7	7	3.4	1	2.4	7	4.7
Any	6	4.7	29	8.4	7	3.9 ^a	20	9.7 ^a	1	2.4 ^b	18	12.2 ^b
Cluster 3												
Compulsive	0	0.0	8	2.3	3	1.7	3	1.4	0	0.0	3	2.0
Passive-aggressive	3	2.3	10	2.9	3	1.7	8	3.9	1	2.4	7	4.7
Dependent	6	4.7	7	2.0	4	2.2	4	1.9	1	2.4	2	1.4
Avoidant	2	1.6	5	1.5	2	1.1	5	2.4	1	2.4	4	2.7
Any	11	8.5	29	8.4	12	6.6	19	9.2	3	7.1	15	10.1
Any personality disorder	23	17.8	74	21.5	30	16.6	46	22.2	5	11.9	37	25.0
Cluster 1 diagnoses only	3	2.3	6	1.7	5	2.8	3	1.4	1	2.4	2	1.4
Cluster 2 diagnoses only	5	3.9	19	5.5	5	2.8	12	5.8	0	0.0	10	6.8
Cluster 3 diagnoses only	10	7.8	19	5.5	9	5.0	14	6.8	2	4.8	10	6.8

^a $\chi^2=5.0$, $df=1$, $p<0.025$.^b $p=0.002$, Fisher's exact test.**TABLE 3. DSM-III Personality Disorders Among Relatives of Probands With Major Depression Grouped by Polarity**

Variable	Unipolar		Bipolar	
	N	%	N	%
Probands	91		17	
Relatives interviewed	356		81	
Relatives with personality disorders				
Cluster 1 diagnoses				
Any	15	4.2	6	7.4
Only	5	1.4	3	3.7
Cluster 2 diagnoses				
Any	26	7.3	8	9.9
Only	18	5.1	5	6.2
Cluster 3 diagnoses				
Any	25	7.0 ^a	12	14.8 ^a
Only	16	4.5 ^b	10	12.3 ^b

^a $\chi^2=5.1$, $df=1$, $p<0.025$.^b $\chi^2=7.3$, $df=1$, $p<0.01$.

the relatives of schizophrenic probands as in the relatives of control subjects.

We have noted previously (29) that the studies providing the strongest support for the inclusion of schizotypal personality disorder in a schizophrenia spectrum have also found schizophrenia to be particularly familial. The schizophrenia label may be applied to some individuals with a highly familial illness and to

others with a relatively nonfamilial illness. Those described here were apparently of the latter sort—the morbid risk for schizophrenia among the relatives of the schizophrenic probands was not significantly higher than that for the relatives of the control subjects (29).

In two studies of the relatives of probands with borderline personality, bipolar affective disorder, or schizophrenia, the prevalence of borderline personality (2) or of borderline, histrionic, or antisocial personality (3) was not found to be higher in the relatives of the probands with bipolar affective disorder. Those negative findings are here extended to include probands with nonbipolar affective disorder. Thus, borderline personality disorder may not be unusually prevalent among relatives of patients with major depression in general despite the now considerable evidence that the relatives of borderline probands are at high risk for major depression (1–4).

This paradox might be explained as follows. Some patients who meet criteria for borderline personality disorder may, in fact, have a highly familial form of affective disorder, while other patients with borderline personality disorder may have an altogether different illness, unrelated to affective disorder. The combined familial loadings for affective disorder would then yield an intermediate value, lower than that for the pure “affective disorder equivalent” group but higher

than that for control probands. If the proportion of individuals with the affective disorder equivalent form of borderline personality is high among patients with borderline personality disorder syndromes but low among patients who present with major depression, then the relatives of the former group would have high rates of affective disorder, while few of the relatives of the latter, affective disorder probands would have borderline personality disorder.

We chose to identify endogenous depression among the probands both clinically and biologically, although we recognize that the validity of either approach is far from settled. Normal DST suppression among probands was significantly associated with cluster 2 or "acting out" personality disorders among relatives. This risk was also higher, but not significantly so, among the relatives of the nonmelancholic depressed probands, and the combination of these indicators in probands put relatives at particularly high risk for these personality disorders. These data qualify in several respects the findings specifically linking borderline personality disorder with affective disorder. First, relatives with antisocial personality and relatives with histrionic personality disorder are as clearly overrepresented in the families of DST suppressors as are relatives with borderline personality disorder. Moreover, biological measures have linked borderline personality to endogenous or melancholic depression—specifically, depressions marked by DST nonsuppression (8, 9) and short REM latencies (6, 7). The present data instead suggest a link between depressions with nonendogenous features and cluster 2 personality disorders in general.

We did not anticipate an association between proband polarity and cluster 3 personality disorders among relatives. There are, in fact, essentially no data on which to base expectations. We therefore give relatively less weight to this finding but present it in case such a relationship emerges in other data sets.

In summary, the present findings support familial links between axis I and axis II disorders but with very modest specificity. There were no clear associations between particular personality disorders and particular axis I disorders. Rather, "acting out" personality disorders in general characterized the families of probands with "nonendogenous" types of depression, and cluster 3 disorders seemed particularly frequent among relatives of bipolar probands. General, rather than specific, findings are not surprising, however, since efforts to rigorously define and validate personality disorders are relatively new. Undoubtedly, these efforts will in time substantially redefine some disorders and will simply fail to validate others.

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The DST in Children and Adolescents With Major Depressive Disorder

Charles D. Casat, M.D., George W. Arana, M.D., and Karin Powell, M.D.

The authors analyzed dexamethasone suppression test (DST) results from 13 prospective studies on the use of the DST in children and adolescents with psychiatric disorders. Sensitivity of the DST was significantly higher among the children than among the adolescents with major depressive disorder (69.6% and 47.1%, respectively), and specificity was significantly lower (69.7% and 80.2%). Significantly more adolescents with major depressive disorder than with other psychiatric diagnoses, especially conduct disorder, were nonsuppressors. The authors discuss possible explanations for the high DST sensitivity among the children and point out the potential usefulness of the DST in differentiating major depressive disorder from conduct disorder.

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The dexamethasone suppression test (DST) has emerged as the most extensively investigated biological test in psychiatry and has been proposed to be diagnostic for the melancholic subtype of major depressive disorder (1-5). Paralleling the interest in the use of the DST in the diagnosis of adult psychiatric disorders, at least 15 studies to date (6-20) have examined the use of the DST in children and adolescents with major depressive disorder and other psychiatric diagnoses. In this paper, we will review findings from these studies and comment on the possible direction of future research with the DST in these age groups.

METHOD

Clinical studies of psychiatric patients younger than 20 years of age were screened for diagnostic method, time and dose of dexamethasone administration, times blood samples were drawn for cortisol determination,

assay method, and use of any concomitant medications. Data were organized for analysis by separating the studies into two age groups: the child group included subjects 5-12 years old (6-10), and the adolescent group included subjects 13-19 years old (11-18).

We reviewed only studies in which a prospective design had been used. Each had used either Research Diagnostic Criteria (21) or DSM-III and included one or more suitable control samples. Where two studies were available from the same investigators and thus may have included data from some of the same subjects, the data were used only from the later study, which reported the larger number of subjects. Data were evaluated and summarized by means of standard statistical techniques across studies by pooling the data (22) and the use of chi-square tests with Yates' correction. Test results were applied to contingency tables for significance.

RESULTS

We included 13 studies in our data analysis. All used the criterion of 5 µg/dl of cortisol to define nonsuppression. Four of the five child studies (6-9) reported administration of 0.5 mg of dexamethasone; the other child study (10) used 20 µg/kg of body weight (or a mean dose of 0.64 mg of dexamethasone). All eight adolescent studies were based on response to 1.0 mg of dexamethasone. Most of the studies assayed serum cortisol at 4:00 p.m. and 11:00 p.m. on the day after dexamethasone administration, although several also included the results of an 8:00 a.m. cortisol sampling time.

All subjects included in the statistical analysis were medication free. Eight subjects in the adolescent group were eliminated because they were receiving concomitant medications (16). One retrospective study of adolescents (19), which used a cortisol criterion of 4 µg/dl, was eliminated because of inadequate information on the diagnoses of the subjects without major depressive disorder. We also excluded data from a study by Doherty et al. (20) because it reported DST results in subjects 3-16 years of age and did not have information sufficient to separate the subjects into child and adolescent groups.

The combined DST sensitivity for major depressive

Received March 4, 1988; revision received Sept. 6, 1988; accepted Sept. 30, 1988. From the Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina. Address reprint requests to Dr. Casat, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

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TABLE 1. Patient and DST Data From Published Studies of Children and Adolescents With Major Depressive Disorder or Other Psychiatric Disorders

Study	Age Range (years)	Diagnostic Criteria	Major Depressive Disorder		Type of Assay ^a	DST ^b	
			N	%		Sensitivity (%)	Specificity (%)
Children (N=145)	5-12		79	54.5		69.6	69.7
Inpatients							
Livingston et al. (6) (N=15)	6-12	DSM-III	3	20.0	RIA	66.6	75.0
Weller et al. (7) (N=68)	6-12	DSM-III	50	73.5	RIA	82.0	72.2
Petty et al. (8) (N=30)	5-12	DSM-III	7	23.3	RIA	85.7	43.5
Outpatients							
Poznanski et al. (9) (N=18)	6-12	RDC	9	50.0	CPB	55.6	88.9
Geller et al. (10) (N=14)	5-12	RDC	10	71.4	RIA	10.0	75.0
Adolescent inpatients (N=475)	13 ^c -19		157	33.1		47.1	80.2
Klee et al. (11) (N=33)	11-17	RDC	20	60.6	CPB	40.0	92.3
Ha et al. (12) (N=42)	13-17	RDC	22	52.4	CPB	31.8	75.0
Targum et al. (13) (N=120)	13-19	DSM-III	17	14.2	RIA	41.2	82.5
Extein et al. (14) (N=27)	14-16	DSM-III	15	55.6	RIA	53.3	91.7
Robbins et al. (15) (N=28)	13-18	RDC	16	57.1	CPB	25.0	100.0
Hsu et al. (16) (N=86) ^d	13-19	DSM-III	14	16.3	RIA	64.3	68.1
Evans et al. (17) (N=55)	12-19	DSM-III	20	36.4	RIA	40.0	80.0
Khan (18) (N=84)	13-17	DSM-III	33	39.3	RIA	47.1	84.3

^aRIA=radioimmunoassay; CPB=competitive protein binding.

^bThe dexamethasone dose in all of the child studies except Geller et al. was 0.5 mg; for the Geller et al. study it was 20 µg/kg of body weight. The dexamethasone dose in all of the adolescent studies was 1.0 mg. In all studies, nonsuppression was defined as postdexamethasone serum cortisol levels greater than 5 µg/dl.

^cTwo studies included adolescents younger than 13 years old: Klee et al. (11) included one adolescent who was 11.2 years old and Evans et al. (17) allowed a cutoff age of 12 years.

^dWe eliminated eight patients because they were taking anticonvulsants (N=6), pemoline (N=1), or clonidine (N=1).

disorder of both groups in the 13 studies was 54.7%, and the specificity was 78.4%. The DST sensitivities and specificities for both groups are presented in table 1. Of 79 children with major depressive disorder, 55 were nonsuppressors, yielding a DST sensitivity of 69.6% and a DST specificity of 69.7%; of 157 adolescents with major depressive disorder, 74 failed to suppress, yielding a sensitivity of 47.1% and a specificity of 80.2%.

The subjects in the child studies were drawn from inpatient (N=113) or outpatient (N=32) populations. Significantly more children with major depressive disorder who were inpatients (81.7%) than those who were outpatients (31.6%) were nonsuppressors ($\chi^2=17.12$, $df=1$, $p<0.00004$). This effect was not seen between inpatient and outpatient children with other psychiatric diagnoses ($\chi^2=2.70$, $df=1$, $p<0.10$). No similar comparison was possible for the adolescent group because all subjects were studied as inpatients.

When we evaluated DST outcome among subjects with major depressive disorder by comparing the use of RDC or DSM-III criteria, we found that 81.7% of the children with major depressive disorder diagnosed by DSM-III and 31.6% diagnosed by RDC were nonsuppressors ($\chi^2=17.12$, $df=1$, $p<0.00004$). For the adolescents, 55.6% of the DSM-III subgroup and 32.8% of the RDC subgroup with major depressive disorder failed to suppress ($\chi^2=7.63$, $df=1$, $p<0.006$).

Although a comparison of DST results between children with major depressive disorder and children in other specific psychiatric diagnostic categories was not

possible because of insufficient data, significant differences in DST results were found between children with major depressive disorder and those with all other psychiatric diagnoses combined and between adolescents with major depressive disorder and those with dysthymia, conduct disorder, schizophrenia, other psychiatric diagnoses, and all other psychiatric diagnoses combined (table 2). The DST specificities for adolescents with dysthymic disorder and for those with conduct disorder were 80.0% and 86.3%, respectively.

DISCUSSION

Numerous variations in methodology were found in the studies reviewed, and many studies had small patient samples. Other methodologic variables included time of serum sampling for cortisol assay (8:00 a.m., 4:00 p.m., 11:00 p.m.), assay method (radioimmunoassay or competitive protein binding), system for establishing diagnosis (structured or unstructured interviews, DSM-III or RDC), and patient status (inpatient or outpatient). There is also the question of multiple diagnoses (major depressive disorder and conduct disorder) among subjects and the effect this may have had on the true versus reported rates of DST nonsuppression for the various diagnostic categories. Because information was lacking in the studies evaluated regarding the presence of other axis I diagnoses, we cannot determine the size of this effect. Conclusions must thus be considered tentative, and more definitive explora-

TABLE 2. DST Results From Published Studies of Children and Adolescents With Major Depressive Disorder or Other Psychiatric Disorders

Group and Diagnosis	DST Non-suppressors		Analysis	
	N	%	χ^2 (df=1)	p ^a
Child (N=145)	75	51.5		
Major depressive disorder (N=79)	55	69.9		
All other diagnoses combined (N=66)	20	30.3	22.26	<0.000002
Adolescent (N=475)	137	28.8		
Major depressive disorder (N=157)	74	47.1		
All other diagnoses combined (N=318)	63	19.8	38.13	<0.0000003
Dysthymia (N=50)	10	20.0	11.58	<0.0007
Conduct disorder (N=102)	14	13.7	30.76	<0.00000005
Schizophrenia (N=26)	6	23.1	5.25	<0.02
Other (N=140)	33	23.6	17.83	<0.00002

^aSignificant difference from major depressive disorder.

tions should be undertaken for clarification of these findings.

Of the 620 subjects included in the studies we reviewed, 236 were diagnosed as having major depressive disorder. The combined sensitivity of the DST for the subjects with major depressive disorder from both groups was 54.7%, which is higher than the 43.1% sensitivity reported by Arana et al. (3) in pooled results of studies of adults with major depressive disorder. Examination of results by age group shows that this variance may be explained by the higher rate of nonsuppression in the children (69.6%) than in the adolescents (47.1%), whose rate was similar to that seen in adults. Specificity for major depression in the children, however, was 69.7%, lower than the rate of 80.2% found in the adolescents or 76.5% reported in adults (3).

The high rate of nonsuppression on the DST for the children could be accounted for by 1) selection of an inappropriate criterion value for defining the significance of postdexamethasone cortisol results, 2) age-related differences in dexamethasone pharmacokinetics, 3) higher basal levels of plasma cortisol in children, 4) age-related differences in nonselective hypothalamic-pituitary-adrenal (HPA) axis response to stress, or 5) an earlier expression of symptoms in a subgroup of children with a high familial loading for major depression, especially of the endogenous type.

The cortisol criterion value (generally 5.0 $\mu\text{g/dl}$) selected to demarcate normal from abnormal DST results contributes significantly to sensitivity and specificity rates (23). This commonly used standard may not be the most appropriate for evaluating the significance of DST results in child studies. The concept of

receiver-operating-characteristic analysis has recently gained favor in evaluating the usefulness of laboratory tests to aid with diagnosis (24). This method of analysis yields a continuous relationship between test sensitivities and specificities that incorporates estimates of random error (25). More detailed reporting of cortisol data (individual subject results rather than means) and use of this analysis in future studies would aid in evaluating the significance of findings and would facilitate comparability between investigations.

In normal adults (26–29) and those with major depressive disorder (27–29), dexamethasone bioavailability shows considerable interindividual variation after administration. Little correlation has been found between dexamethasone levels attained and body surface area in adults, and reports of a relationship to body weight have been contradictory (20, 28–30). Although dexamethasone levels during the early absorption phase appear indistinguishable between suppressors and nonsuppressors, more rapid elimination is seen in nonsuppressors (30). An inverse relationship between dexamethasone level and cortisol outcome has been described in adult subjects with major depressive disorder (26–29, 31–35). No studies of dexamethasone bioavailability have been done in children or adolescents.

Stable circulating cortisol levels are established in the second year of life (36) and do not vary substantially from basal levels in adults. It is unlikely, therefore, that the higher rate of nonsuppression in the child studies is associated with age-related differences in the basal functioning of the HPA axis. A relationship between high basal cortisol levels and nonsuppression on the DST has been reported in some studies of adults with major depressive disorder (37, 38); others (39) have not found such a correlation. Doherty et al. (20) found no significant differences in basal cortisol values between suppressors and nonsuppressors in children aged 3–16 years who were hospitalized on a psychiatric inpatient unit. Puig-Antich et al. (40) reported higher basal cortisol levels in children with endogenous major depressive disorder than in control subjects but did not examine the rate of nonsuppression on the DST as a function of basal cortisol levels.

Various stressors have been demonstrated to provoke a large transient rise in cortisol production (41). Tennes and Kreye (42) reported that grade-school children had significantly higher spot urinary cortisol levels on mornings when examinations were anticipated than on other days. Those children with poor social skills were found to have the greatest increases in cortisol.

Hospitalization has been shown to increase the rate of nonsuppression on the DST in the first 48 hours after admission among adult psychiatric and medical patients (43). In the studies that we reviewed, the rate of nonsuppression in inpatient children with major depressive disorder was significantly higher than in outpatient children with major depressive disorder, a finding that may be a hospitalization effect or that

may reflect greater severity of illness among inpatients. The difference in the rate of nonsuppression in subjects with other diagnoses failed to reach significance, suggesting the possibility of an interaction between diagnosis and response to the stress of hospitalization. A study of serial DST responses in children admitted for various psychiatric disorders would help to determine the influence of hospital admission on cortisol production.

Among adults, familial loading for affective disorder increases the rate of postdexamethasone cortisol nonsuppression (44). Puig-Antich (45) noted a high (0.42) familial loading for major depressive disorder in adult relatives of male probands with prepubertal major depressive disorder. The high rate of nonsuppression found in the child studies we reviewed could partially be the result of early symptom expression in a selective group of children with a high familial loading for major depressive disorder. Investigation of correlations between DST results and prevalence of major depressive disorder among adult relatives of child and adolescent probands with major depressive disorder should help to resolve this issue.

In the adolescents, nonsuppression on the DST differentiated major depressive disorder from conduct disorder (with a specificity of 86.3%). Because conduct disturbance is the most common initial complaint in 35%–40% of children (46) and adolescents (47) with major depressive disorder, the DST should be evaluated for its potential to identify patients with major affective disorder whose initial symptoms are behavioral.

In summary, analysis of data from studies of the DST in children and adolescents with major depressive disorder revealed a higher rate of nonsuppression among the children than among the adolescents or adults. Further research on HPA axis dysregulation and dexamethasone metabolism in children and adolescents is needed to clarify these differences and assess whether the DST may be useful in diagnosis and prediction of treatment outcome.

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Ability to Form an Alliance With the Therapist: A Possible Marker of Prognosis for Patients With Antisocial Personality Disorder

Linda Gerstley, Ph.D., A. Thomas McLellan, Ph.D., Arthur I. Alterman, Ph.D.,
George E. Woody, M.D., Lester Luborsky, Ph.D., and Maurice Prout, Ph.D.

Antisocial personality disorder is generally perceived to be refractory to treatment, particularly psychotherapy. In this study, the ability of 48 patients with this disorder to form a working relationship with a psychotherapist or drug counselor was examined in relation to outcome of 24 weeks of treatment evaluated at 7-month follow-up. Some antisocial patients were able to form working relationships with their therapists, and there was a significant association between the ability to form such a relationship and treatment outcome. Measures of this ability, such as the Helping Alliance Questionnaire, may help identify antisocial patients who can benefit from psychotherapy.

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The diagnostic framework for antisocial personality disorder in *DSM-III* (and more recently in *DSM-III-R*) depends primarily on behavioral indicators such as truancy early in the school years, unstable work performance, and criminality. To receive the *DSM-III* diagnosis, an individual must demonstrate a certain number of these types of behaviors, in any combination, both before and after age 15. However, some clinicians contend that focusing exclusively on behavioral measures may neglect important underlying personality structures and may result in giving this diagnosis to a relatively heterogeneous group of individuals in terms of their personality dynamics. In this regard, it has been suggested by several authors (1-3) that there are "primary" antisocial individuals whose antisocial behaviors are the result of an underlying personality structure, and there is a more healthy group whose antisocial behaviors are "secondary" to other problems, such as fear of loss, narcis-

sistic injury, or even substance abuse. According to these theorists, the distinctions between individuals with primary and secondary antisocial personality disorders would not be found in their antisocial behavior patterns, which would be common to both groups, but rather in their underlying personality characteristics, such as inability to empathize, inability to experience guilt, and, particularly, inability to develop meaningful human relationships.

There is now a body of research on many types of patients that confirms an association between a patient's ability to form meaningful relationships and psychotherapy outcome (4, 5). However, this issue has not been explored systematically in patients with antisocial personality disorder. Despite the lack of confirmatory research, the inability to form meaningful human relationships has been considered by many to be a cardinal feature of "primary sociopaths" (1-3) and has been considered one of the major reasons for their generally poor therapeutic outcome (6, 7). Although the *DSM-III* and *DSM-III-R* diagnostic criteria for antisocial personality disorder include inability to sustain a totally monogamous relationship for more than 1 year as one of the prototypic features, inability to form meaningful relationships is not a specific requirement for the diagnosis. Thus, the *DSM-III* and *DSM-III-R* criteria for antisocial personality disorder may underemphasize a central element of the disorder, one that may be importantly related to treatment response. In other words, by failing to make the personal characteristic of severe difficulty in interpersonal relationships a requirement for a positive diagnosis, *DSM-III* and *DSM-III-R* may be failing to distinguish between individuals with antisocial *behavior*, who might benefit from psychotherapeutic treatment, and those with antisocial *personality*, who are much less likely to benefit.

While there is disagreement concerning the definition of antisocial personality disorder, most therapists agree that its presence is indicative of a poor treatment outcome. Perhaps the least successful intervention attempted with this kind of patient has been individual psychotherapy. The published literature on the subject is sparse, but clinical experience and anecdotal reports suggest that the

Received Oct. 13, 1987; revisions received June 20 and Sept. 6, 1988; accepted Oct. 7, 1988. From the Departments of Psychiatry, Philadelphia VA Medical Center and the University of Pennsylvania, and the Department of Mental Health Sciences, Hahnemann University, Philadelphia. Address reprint requests to Dr. McLellan, Bldg. 7, Philadelphia VA Medical Center, University Avenue, Philadelphia, PA 19104.

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psychotherapeutic approach is generally contraindicated. According to Kernberg (7), "There is nothing new in mentioning the absolutely hopeless prognosis for the analytic treatment of antisocial personalities" (p. 254), and a similar sentiment seems to exist among those who use less traditional psychotherapeutic approaches. For example, it is common practice among many substance abuse programs to deny psychotherapeutic treatment to opiate abusers, in large part because of an assumption that opiate addicts are likely to have antisocial personality disorder and will therefore not benefit from psychotherapeutic treatment.

Given the stigma and the poor treatment prognosis associated with this disorder, it becomes extremely important to examine heterogeneity within the current *DSM-III* and *DSM-III-R* category in order to identify those patients who meet the current diagnostic criteria for the disorder but who may nevertheless benefit from treatment (8, 9). For example, Woody et al. (10) showed that at least some opiate abusers who met the *DSM-III* criteria for antisocial personality disorder could respond to a 6-month course of professional, individual psychotherapy. These investigators found that a lifetime diagnosis of depression differentiated the patients who were able to benefit from psychotherapy from those who showed essentially no gains.

We found this initial report intriguing, and in light of the negative prognosis generally associated with the diagnosis of antisocial personality disorder and the controversy concerning the *DSM-III-R* criteria for diagnosis of the disorder, we undertook the present study to reexamine the data from the Woody et al. psychotherapy study (10–12). We hypothesized that since psychotherapy is an interpersonal process, differences in the ability to form relationships could be an important factor in the identification of patients with antisocial personality disorder who are able to respond positively to psychotherapy. Thus, the present research explored the extent to which the capacity to form a relationship with the therapist, measured by the Helping Alliance Questionnaire (13), was related to 7-month outcome of psychotherapy in patients who met the *DSM-III* criteria for antisocial personality disorder. Two questions were posed: 1) Was there variability among these patients in their capacity to form a helping relationship with the therapist, or were they uniformly lacking in this capacity? 2) Was the ability to form a helping relationship related to positive outcome following treatment among the patients who received 24 weeks of individual psychotherapy?

METHOD

The data we used were collected as part of the Woody et al. psychotherapy study, the design and results of which have been detailed elsewhere (10–12, 14). In that study, 110 methadone-maintained male opiate addicts were randomly assigned to three treat-

ment groups: 1) drug counseling only, 2) supportive/expressive psychotherapy plus drug counseling, and 3) cognitive/behavioral psychotherapy plus drug counseling. Psychotherapy was provided once each week for 6 months (24 sessions). All diagnoses were made using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (15). Only experienced clinicians made the diagnoses, and all of them received the standard instructional package, including training test tapes, as a means of maintaining reliability and validity. To assess treatment effects, data on a range of patient outcome measures were collected 7 months after treatment by independent technicians using the Addiction Severity Index, a comprehensive assessment interview with demonstrated reliability and validity (16, 17).

Of the 110 subjects included in the Woody et al. study, 53 received a *DSM-III* diagnosis of antisocial personality disorder according to the SADS-L interview. All of these 53 subjects also received a *DSM-III* diagnosis of opiate dependence, and 27 subjects received at least one additional axis I diagnosis (16, major or intermittent depressive disorder; seven, generalized anxiety disorder; four, miscellaneous diagnoses). No subject in this study received an additional axis II diagnosis. The 57 subjects who did not receive a diagnosis of antisocial personality disorder were excluded from the present study. Data from an additional five subjects were lost at follow-up, reducing the total number of subjects with complete data to 48.

Table 1 provides additional descriptive data on the 48 subjects included in this study. On average, these patients were in their mid-30s and had been addicted to opiates for approximately 12 years. Most had had at least a high school education or its equivalent. The majority were not currently married. Most of the patients were not working during the month prior to admission. Virtually all reported that they had previously been treated for their addiction, and most indicated that they had been in methadone maintenance treatment before.

Thirty-one (65%) of these patients had been randomly assigned to individual psychotherapy (cognitive/behavioral or supportive/expressive) as well as drug counseling. The remaining 17 patients had received only drug counseling. Thus, it was possible to examine the relationships between "counseling alliance" and treatment outcome in all 48 subjects and the relationships between "therapist alliance" and treatment outcome in 31 subjects.

The Helping Alliance Questionnaire (13) contains 12 items that estimate the degree to which the respondent experienced a "therapeutic" relationship as helpful. Items were rated on Likert scales and summed to produce a total score, which ranged from 0 to 96 in this sample. A body of previous research in psychotherapy by Luborsky and others (5, 14, 18) has examined the development of relationships within the therapeutic setting by means of the Helping Alliance

TABLE 1. Demographic Data on 48 Male Patients With Antisocial Personality Disorder and Opiate Dependence

Variable	N	%
Race		
Black	25	52
White	23	48
Marital status		
Never married	16	33
Divorced/separated	22	46
Married/common-law marriage	10	21
Education		
Less than high school	6	12
High school/General Equivalency Diploma	28	58
Some college	14	30
Living arrangement		
With parents	14	30
With spouse/other	10	21
With others	18	37
Alone	6	12
Employment income		
Yes	20	42
No	28	58
Welfare income		
Yes	16	33
No	32	67
Past drug treatment		
Yes	45	95
No	3	5
Past methadone treatment		
Yes	42	88
No	6	12
Arrested in last 6 months		
Yes	10	21
No	38	79
Parole, probation, or legal case pending		
Yes	21	44
No	27	56

Questionnaire. This brief instrument is administered to the patient and therapist/counselor after the third psychotherapy/counseling session and provides an estimate of the strength and quality of the therapeutic alliance at that point. In this study, parallel forms were used to assess patients', therapists', and drug counselors' views of the therapeutic relationships following the third treatment session. Thus, there were four measures of the helping alliance: 1) the patient's rating of his relationship with his drug counselor, 2) the patient's rating of his relationship with his therapist, 3) the drug counselor's rating of his relationship with the patient, and 4) the therapist's rating of his relationship with the patient.

The Addiction Severity Index (16, 17) is a clinical research interview designed to assess the severity of problems in seven areas of functioning commonly associated with treatment problems in alcohol and drug abuse patients: medical, legal, alcohol abuse, drug abuse, employment, family/social, and psychological. This index was completed by an independent technician at baseline and at 7-month follow-up. Six composite scores (drug, alcohol, employment, legal, medical, and psychiatric) derived from the 7-month follow-up interview were used as outcome measures.

RESULTS

Since the data resulted from an earlier study involving three separate treatment groups (10–12), it was important to determine whether there were differences in the results on the measures among the subjects from the three initial treatment groups. One-way between-groups analysis of variance was used to compare the subjects from the original treatment groups on scores on the Helping Alliance Questionnaire and the six baseline composite measures from the Addiction Severity Index. Results of these analyses confirmed that there were no differences among the subjects from the three original groups on any of these measures ($p > 0.10$ on all comparisons), and we were therefore at liberty to combine subjects from the original two types of psychotherapy groups in subsequent analyses.

Table 2 shows the changes from baseline to 7-month follow-up in scores on each of the Addiction Severity Index composite measures. Paired t tests were used to assess the degree of change on each measure; as can be seen, there was evidence of significant improvement on the drug, employment, and legal status measures.

We then used autoregression (baseline to 7-month follow-up) to partial out the influence of the baseline status on scores on each of the six Addiction Severity Index composite measures. This procedure corrected for intersubject differences in pretreatment status, thus enabling a more direct assessment of the effects of the Helping Alliance Questionnaire ratings on outcome. The residual score on each measure for each subject was saved for use as an "adjusted" outcome score in all subsequent analyses. We then examined whether there was a significant overall relationship between any of the four helping alliance measures and the set of six adjusted outcome measures. To this end, multiple correlations were calculated between each helping alliance measure and the full set of adjusted outcome measures. It was reasoned that a significant ($p < 0.05$) overall correlation between a helping alliance measure and the set of adjusted outcome criteria would provide justification for additional analyses among specific helping alliance measures and specific types of outcome.

As can be seen in Table 3, two of these multiple correlations (therapist's assessment of alliance and patient's assessment of alliance with therapist) were significant, indicating that both the patient's and the therapist's perceptions of the helping alliance were significantly related to overall outcome. On the other hand, although there was a trend toward significant relations between the full outcome set and the patient's and the counselor's perceptions of the counselor relationship, neither the patient's nor the counselor's perception of the quality of their relationship was significantly correlated with the set of six adjusted outcome measures. Therefore, in the next phase of data analysis only the patient's and therapist's assessments of their relationship were correlated with the specific adjusted outcome measures.

TABLE 2. Scores on Composite Outcome Measures of 48 Patients With Antisocial Personality Disorder and Drug Dependence Who Received Psychotherapy and Drug Counseling or Drug Counseling Only

		Score ^a						
Composite Measure From the Addiction Severity Index	N	Baseline		7-Month Follow-Up		t ^b	df	p
		Mean	SD	Mean	SD			
Drug	48	0.20	0.12	0.14	0.14	2.38	46	<0.03
Alcohol	47	0.11	0.14	0.11	0.18	0.20	45	n.s.
Employment	48	0.43	0.18	0.34	0.22	2.40	46	<0.03
Legal	48	0.21	0.19	0.15	0.19	2.03	46	<0.05
Medical	48	0.29	0.28	0.33	0.35	0.32	46	n.s.
Psychiatric	47	0.17	0.12	0.15	0.14	0.18	45	n.s.

^aScores reflect status during the 30-day periods before treatment and before follow-up, with higher values indicating worse status.

^bFor paired observations, two-tailed probabilities.

TABLE 3. Multiple Correlations of Helping Alliance Measures With Overall Outcome for Patients With Antisocial Personality Disorder and Opiate Dependence Who Received Psychotherapy and Drug Counseling or Drug Counseling Only

Helping Alliance Measure	N	R ^a	df	p
Patient-psychotherapist alliance				
Therapist's assessment	31	0.68	6, 24	<0.001
Patient's assessment	31	0.64	6, 24	<0.001
Patient-counselor alliance				
Counselor's assessment	42	0.31	6, 35	<0.09
Patient's assessment	42	0.34	6, 35	<0.07

^aMultiple correlation between the complete set of adjusted outcome variables (Addiction Severity Index drug, alcohol, employment, legal, medical, and psychiatric measures) and each therapeutic alliance measure. Probabilities are two-tailed.

Table 4 shows the correlations for these two helping alliance measures. The therapist's perception of the quality of the therapeutic alliance was significantly correlated with the patient's employment status at 7-month follow-up, and the correlation of the therapist's perception with the patient's medical and psychiatric status at follow-up approached significance. The patient's perception of the quality of the alliance with his therapist was significantly correlated with decreased drug use and improved employment status at follow-up. Additionally, the correlations between this alliance measure and legal and psychiatric status at follow-up approached significance.

DISCUSSION

Neither the counselor's nor the patient's assessment of the counseling relationship was significantly related to overall outcome, although there was the suggestion of a general trend in that direction. On the other hand, a positive assessment of the therapeutic alliance by either the patient or the psychotherapist was significantly related to improvements in overall functioning, as indicated by the multiple correlation coefficients. The finding that a positive assessment of the helping alliance between a therapist and a patient with antisocial personality disorder was associated with reduced drug use and increased employment is particularly important because these are major goals of treatment. Of

TABLE 4. Correlations Between Patient-Psychotherapist Helping Alliance and Adjusted Composite Outcome Measures for 31 Patients With Antisocial Personality Disorder and Drug Dependence Who Received Psychotherapy and Drug Counseling

Composite Measure From the Addiction Severity Index	Therapist's Rating of Helping Alliance				Patient's Rating of Helping Alliance			
	N	r	df	p ^a	N	r	df	p ^a
Drug	31	0.19	29	n.s.	31	0.40	29	<0.05
Alcohol	30	0.05	28	n.s.	30	0.21	28	n.s.
Employment	31	0.41	29	<0.04	31	0.50	29	<0.01
Legal	29	0.00	27	n.s.	29	0.32	27	<0.10
Medical	31	0.34	29	<0.10	31	0.26	29	n.s.
Psychiatric	29	0.21	27	<0.12	29	0.27	27	<0.10

^aProbabilities are two-tailed.

course, it should be clear that the nature and extent of the changes among these patients were not as large or as pervasive as the changes among the other diagnostic subgroups studied by Woody et al. (10). However, these antisocial personality disorder patients did show positive change, and this was still evident at 7-month follow-up. In the earlier study (10) we had seen evidence of positive change as a result of psychotherapy among the antisocial patients who had additional *DSM-III* diagnoses of major or intermittent depressive disorder. We had hoped to explore this finding further in the present study, but the number of therapy patients with both antisocial personality disorder and depression in our sample was too small to examine.

Neither patient nor therapist assessment of the therapeutic alliance was associated with reduced psychiatric symptoms. In this regard, it should be noted that the Addiction Severity Index measure of psychiatric severity mainly reflects the presence of "psychiatric symptomatology" such as depression, anxiety, and thought disturbance. The levels of these symptoms in this antisocial personality disorder sample were relatively low at the beginning of treatment and were not significantly lower following treatment (table 2). This may account in some part for the low correlation between the therapeutic alliance measure and change in psychiatric status.

These results suggest that the therapist relationship factors that have been associated with response to psychotherapy in other patient samples and in other diag-

nostic groups (5) are also important for antisocial patients. Several factors are known to be correlated with the development of a positive therapeutic alliance in patients who are not antisocial: demographic similarities between patient and therapist (13), therapist activity (13), degree of patient involvement in therapy as rated by a clinical observer (19), the therapist's positive regard and understanding as rated by the patient (20), mutual patient-therapist understanding as rated by the patient (18), and patient likability (21). In this regard, the findings of this study are consistent with past research and extend the earlier work by suggesting two new findings. First, even patients with a *DSM-III* diagnosis of antisocial personality disorder were not uniformly lacking in the capacity to form a therapeutic alliance. Second, even among these patients who have a particularly poor prognosis, the ability to develop a therapeutic (helping) alliance was significantly associated with improvement following professional psychotherapy.

CONCLUSIONS

The findings of this research lend support to the idea that some patients who meet the *DSM-III* criteria for antisocial personality disorder are capable of forming a meaningful relationship with a therapist and thus are able to benefit from psychotherapy. It must also be stated that the *DSM-III* diagnosis of antisocial personality disorder did distinguish patients with poorer outcomes of psychotherapy from patients with other diagnoses (e.g., depression [10]), and the focus on antisocial behaviors has made this one of the most reliably diagnosed (in terms of intertherapist agreement) of all *DSM-III* disorders (Endicott, personal communication, 1987). However, the work reported here suggests that within the current *DSM-III-R* diagnostic category of antisocial personality disorder, it may be possible to develop an even more accurate indication of therapy prognosis—a need that has been emphasized by Guze (22), Garfield (23), and Whitters et al. (8, 9)—by attending to the quality of the patient's relationship formation. At present, the widely held convention of denying psychotherapy to subgroups of individuals who may have antisocial personality disorder (e.g., substance abusers, prison inmates) may exclude some patients with antisocial behaviors who might nevertheless benefit from psychotherapy. Unless and/or until these diagnostic criteria are revised, treatment decisions concerning patients with antisocial personality disorder might be more appropriately made after a "trial run" of three or four therapy sessions. At that point, both the patient and the therapist should decide whether the relationship is worth continuing. Future studies, with larger samples, may address this issue and explore additional factors such as other patient characteristics, patient-therapist "match," and therapy process variables that may facilitate the devel-

opment of a therapeutic alliance in these particularly difficult patients.

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A Controlled Trial of Desipramine in 18 Men With Posttraumatic Stress Disorder

Christopher Reist, M.D., Curtis D. Kauffmann, M.D., Richard J. Haier, Ph.D.,
Christopher Sangdahl, M.D., Edward M. DeMet, Ph.D.,
Aleksandra Chicz-DeMet, Ph.D., and James N. Nelson, M.D.

Eighteen male U.S. veterans meeting DSM-III criteria for posttraumatic stress disorder (PTSD) completed a 4-week double-blind, crossover study comparing administration of 200 mg/day of desipramine with placebo. Response was measured by using the Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Impact of Event Scale. Overall, the only apparent response to desipramine was in some symptoms of depression; there were no changes in anxiety and other PTSD symptoms.

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The syndrome of posttraumatic stress disorder (PTSD), as defined by DSM-III, encompasses a wide variety of symptoms. These include intrusive recollections of the traumatic events, social avoidance, autonomic dysfunction, and cognitive disturbances. Symptoms of affective disorder, such as depressed mood, sleep disturbance, and loss of interest in usual activities, are also often prominent.

DSM-III places PTSD in the diagnostic category of anxiety disorders in which "anxiety is either the predominant disturbance . . . or anxiety is experienced if the individual attempts to master the symptoms, as in

confronting the dreaded object or situation" (p. 225). A relationship of PTSD to affective illness has been suggested by family and concurrent illness studies (1-3). A family study by Davidson et al. (1) revealed a 20% incidence of depression in first-degree relatives of probands with PTSD diagnosed according to DSM-III criteria. In the same study, 41% of the probands had histories consistent with "nonbipolar" depression and 25% gave histories of bipolar illness. Sierles et al. (2, 3) found some form of depression (e.g., major depression, dysthymia, cyclothymia) to be present in the histories of 72% of a group of 25 inpatients with PTSD and 84% of a group of 25 outpatients with PTSD.

Also consistent with the relationship of PTSD to affective disorder are a number of uncontrolled clinical trials demonstrating modest, positive therapeutic response to monoamine oxidase inhibitors (4-6) and various tricyclic antidepressants (7-9). Bleich et al. (10) retrospectively reviewed the cases of 25 patients with PTSD treated with antidepressants and found that 67% had good to moderate responses of PTSD symptoms other than depression. Frank et al. (11) conducted a placebo-controlled trial of imipramine and phenelzine in 23 outpatient veterans with PTSD. Both drugs significantly improved both PTSD and depressive symptoms. In another controlled trial, however, Shestatsky et al. (12) found that the effects of phenelzine did not differ from those of placebo.

Our own experience with PTSD patients has included an uncontrolled study of desipramine in eight male U.S. veterans (13). We found significant improvement in Hamilton and Beck depression scale scores in these patients ($p < 0.05$, two-tailed t test). Although the clinical response in PTSD symptoms was not significant for the whole group, half of the sample showed a greater than 25% improvement in their PTSD symptoms as measured by the Impact of Event Scale. These

Received June 22, 1987; revisions received March 28 and Sept. 6, 1988; accepted Sept. 22, 1988. From the Department of Psychiatry, VA Medical Center, Long Beach, and the Department of Psychiatry, University of California, Irvine. Address reprint requests to Dr. Reist, Psychiatry Service, VA Medical Center, 5901 East 7th St., Long Beach, CA 90822.

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findings encouraged us to undertake a double-blind, crossover trial comparing desipramine with placebo in the treatment of PTSD.

METHOD

The patient sample originally comprised 27 hospitalized men aged 28–64 years ($\text{mean} \pm \text{SD} = 38.4 \pm 6.0$) who were diagnosed as having PTSD according to *DSM-III* criteria. Patients were Vietnam combat veterans, except for one World War II veteran, referred from our outpatient psychiatry service and by local Vietnam veterans outreach centers between September 1986 and February 1987. All individuals had been free of medication and drugs for a minimum of 1 week before the study began. Patients with a history of alcohol use had been abstinent for at least 2 weeks before the study. None of these individuals experienced alcohol withdrawal symptoms.

Before beginning treatment, patients gave informed consent and completed a physical examination, ECG, and standard laboratory tests that included thyrotropin (TSH), T_3 (resin uptake), and T_4 . PTSD symptoms were assessed by using the Impact of Event Scale (14, 15). In addition, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Beck Depression Inventory were completed. Concurrent axis I and axis II diagnoses were established through use of the Structured Clinical Interview for *DSM-III* (16) and the Structured Clinical Interview for *DSM-III-R* (17) for personality disorders. The interviews were conducted by two of us (C.D.K. and C.R.).

Following this workup during the first week of hospitalization, patients were randomly assigned to treatment with desipramine or placebo (double-blind). Patients were treated with oral desipramine at a beginning dose of 50 mg/day. This was increased daily by 50-mg increments to a maximum dose of 200 mg/day. Although the maximum intended dose was 200 mg/day, fluctuations in the intended regimen due to the development of side effects in some patients produced a mean maximum dose of 165 ± 22.5 mg/day (range = 100–200 mg/day). The $\text{mean} \pm \text{SD}$ length of treatment at maximum dose was 25 ± 3 days. After 4 weeks of treatment, patients were switched to the alternate drug (desipramine or placebo) during a 4-day crossover period. Placebo and active drug capsules were switched one for one, and the patients were treated for an additional 25 days. Following the initiation of treatment during the first phase, patients received four capsules daily. Medication was ingested in the presence of the medication nurse. The Impact of Event Scale, the Hamilton scales, and the Beck scale were repeated at weekly intervals throughout the study.

All patients participated in daily ward activities that included recreational and group therapies. Physician contact was exclusively for rating scale interviews and medication evaluation. Patients did not receive individual psychotherapy.

Blood samples were drawn at the end of each treatment phase for measurement of plasma desipramine (determined at the end of the study). Blood specimens were collected in venipuncture tubes containing EDTA as the anticoagulant and immediately centrifuged to separate plasma. Samples were stored at -70°C in polypropylene tubes until assayed at the end of the study. Desipramine levels were determined by the fluorescence polarization immunoassay method (18); the automated Abbott TDx analyzer (Abbott Laboratories, North Chicago, IL) was used. The Abbott TDx tricyclic antidepressant assay has a sensitivity of 20 ng/ml (the smallest single value that can be distinguished from zero at the 95% confidence limit) and a coefficient of variation of less than 8% at the level of 100 ng/ml.

Of the 27 original patients, 21 completed the crossover period. Six patients dropped out for the following reasons: one patient left the hospital against medical advice; one patient was excluded for continued substance abuse; two patients developed irritability and dysphoria while taking desipramine; and, during the workup period, one patient developed mania and one patient became intolerant of the ward structure and asked to be withdrawn. Desipramine levels of less than 1.0 mg/ml were found in two additional patients, and technical difficulties precluded measurement in one patient. These three patients were also excluded from the analysis, leaving a sample of 18 patients.

RESULTS

Most of the 18 patients with PTSD who completed the study also met *DSM-III* criteria for disorders other than PTSD. Sixteen of the patients had at least one affective disorder; six of these met criteria for major depression. Alcohol or substance abuse were diagnosed in 11 patients. Other axis I diagnoses included dysthymic disorder ($N=9$), generalized anxiety disorder ($N=2$), cyclothymia ($N=3$), and somatization disorder ($N=1$).

Following termination of the study, blood samples collected at the end of each treatment phase were analyzed for desipramine. Results showed a mean serum level of 107.3 ± 76.0 ng/ml (range = 0–291, excluding two patients with levels below 1.0 ng/ml and one who could not be assayed). For the group, there was a rank correlation ($\rho=0.46$, $N=18$, $p<0.05$, one-tailed) between desipramine blood level and the percent change in Hamilton depression scale ratings during the drug phase. Table 1 presents the mean rating scale scores for the desipramine and placebo treatment conditions before and after drug or placebo administration. Separate three-way analyses of variance (ANOVAs) for each rating scale revealed significant effects only for the Hamilton depression scale and the Hamilton anxiety scale. For the Hamilton depression scale there was a main effect for time (before versus after drug or placebo administration) ($F=4.93$, $df=1, 16$, $p=0.041$) and interactions between Drug Status (desipramine

TABLE 1. Ratings of 18 Men With Posttraumatic Stress Disorder on Five Scales Before and After Administration of Desipramine and Placebo

Scale	Desipramine				Placebo			
	Before		After		Before		After	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hamilton Rating Scale for Depression	19.8	10.5	15.0	9.5	16.9	8.3	17.2	9.1
Hamilton Rating Scale for Anxiety	15.5	10.0	14.0	10.5	17.1	9.2	15.1	10.8
Beck Depression Inventory	27.0	14.1	26.5	16.3	30.2	13.4	29.2	16.2
Impact of Event Scale								
Avoidance	26.5	10.3	26.1	9.1	27.7	6.2	27.6	10.0
Intrusion	28.7	7.4	27.7	8.6	28.5	8.3	28.1	7.9

versus placebo) by Order (desipramine first versus placebo first) ($F=10.17$, $df=1, 16$, $p=0.005$), Drug Status by Time ($F=4.62$, $df=1, 16$, $p=0.04$), and Drug Status by Time by Order ($F=6.18$, $df=1, 16$, $p=0.03$). Post hoc t tests showed that Hamilton depression scale scores were significantly lower after drug or placebo administration only in the desipramine-first group ($t=2.86$, $df=7$, $p=0.02$, two-tailed). Using a 50% drop in Hamilton depression scale score as a criterion for response, we determined that five patients in the desipramine condition responded; three patients responded during placebo treatment. For the Hamilton anxiety scale, only a main effect for time was significant ($F=5.66$, $df=1, 16$, $p=0.03$).

Because we had no observer-rated scales of PTSD, items from the Hamilton depression and anxiety scales were selected post hoc that we felt were most relevant to PTSD symptoms. This was done blind to individual scores. We found no significant difference in scores on these items between the drug and placebo conditions.

A separate analysis was done on the six patients who met *DSM-III* criteria for major depression. As expected, treatment with desipramine was superior to placebo in improving these patients' depressive symptoms, measured by the Hamilton depression scale (mean changes in scores of 4.0 after desipramine and -3.0 after placebo; $t=2.43$, $df=5$, $p=0.02$, two-tailed). Scores on the other rating scales showed no significant change, although scores on the Impact of Event Scale intrusion subscale improved marginally ($p=0.09$, n.s.).

DISCUSSION

Overall, desipramine did not produce dramatic effects for these PTSD patients, although their depressive symptoms were significantly ameliorated, especially when desipramine was given at the beginning of hospitalization. The effects of desipramine, however, were apparent only on the physician rating of depression, not the self-report. The fact that depressive symptoms responded to treatment suggests that drug levels and duration of treatment were adequate to realize a clinical improvement. In spite of this, a lack of improvement in PTSD symptoms was apparent in all patients, including those who had desipramine blood levels

higher than 100 ng/ml. We used relatively modest doses and only 4 weeks of treatment, however; it is possible that the PTSD symptoms may have resolved with higher doses and longer treatment.

The high incidence of concurrent psychiatric diagnoses found in these patients is in agreement with other reports (1, 3) and suggests that PTSD patients form a very heterogeneous group. Sierles et al. (3) emphasized the importance of considering other *DSM-III* diagnoses and questioned whether improvement in PTSD symptoms is actually due to alleviation of concurrent illness. The present findings suggest that the symptoms of depression and PTSD may be independent or that desipramine treatment is symptom specific.

The heterogeneity of PTSD patients may explain the variable and inconclusive findings of previous investigations of pharmacological treatment. The modest statistically significant improvement of depressive symptoms in our PTSD patients suggests that desipramine may be of some therapeutic benefit for such patients, although desipramine may not alleviate the primary symptoms of PTSD.

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The Manfred S. Guttmacher Award

The American Psychiatric Association and the American Academy of Psychiatry and the Law invite applications for the 1990 Manfred S. Guttmacher Award. This award is given for an outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work presented at a professional meeting or published between May 1, 1988, and April 30, 1989. The award will be cited in the Convocation of Fellows program of the 1990 APA Annual Meeting. The date and place of the formal presentation of the award will be announced at a later date. The recipient is expected to give an award lecture. The award includes an honorarium of \$500 and a plaque. The travel expenses of a nonmember winner will be reimbursed up to \$500.

Anyone wishing to apply should submit six copies of the work, along with six copies of an abstract, to William H. Reid, M.D., M.P.H., Chairman, Guttmacher Award Board, American Psychiatric Association, 1400 K Street, N.W., Suite 327, Washington, D.C. 20005.

Entries must be received by May 15, 1989. Entries will be acknowledged but not returned.

Infrequent Occurrence of EEG Abnormalities in Panic Disorder

Murray B. Stein, M.D., and Thomas W. Uhde, M.D.

EEG abnormalities have been frequently reported in patients with panic disorder, although controlled studies are lacking. The authors examined the EEGs of 35 consecutively evaluated, medication-free patients with panic disorder and found that only five (14%) had nonspecific abnormal EEGs and none displayed EEG evidence supportive of an ictal process. The presence or absence of EEG abnormalities was not significantly associated with the presence or absence of psychosensory symptoms. Although it is not likely that panic disorder is an epileptiform disorder, temporal lobe and limbic structures probably play a major role in the pathophysiology of panic.

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The protean somatopsychic manifestations of panic disorder can resemble the symptoms of cardiac, respiratory, neurologic, and other diseases (1, 2). In particular, many patients with panic disorder have been noted to experience transient sensory, cognitive, and emotional phenomena similar to those occurring in individuals with partial complex seizures (3, 4). In addition, a number of case reports have suggested that some patients with panic attacks may have abnormal EEGs and that a subgroup of these patients may respond to treatment with anticonvulsants (5-7). Furthermore, a large body of experimental and clinical data has suggested that fear episodes may occur as an ictal symptom in patients with temporal lobe epilepsy (8, 9) or as a result of electrical stimulation of the temporal lobe with depth electrodes (10, 11).

Taken together, these observations suggest that panic disorder may be intimately related to temporal lobe epilepsy. Nonetheless, although case reports abound, to date we know of no studies that have examined EEG results in a series of patients with panic disorder. Therefore, we examined the prevalence of EEG abnormalities and their relationship to psycho-

sensory symptoms in 35 drug-free patients with panic disorder.

METHOD

We evaluated a consecutive series of outpatients (N=24) and inpatients (N=11) who met Research Diagnostic Criteria (12) for panic disorder. The mean \pm SD age of the 35 patients (24 women, 11 men) was 35 ± 8 years; 33 had been free of all psychotropic drugs for a minimum of 2 weeks before their EEGs, and the other two patients were evaluated 2 days after completing withdrawal from a low dose of a benzodiazepine. The mean \pm SD duration of illness of the 35 patients before evaluation was 8.9 ± 5.4 years.

EEGs were performed in the customary manner over 45 to 75 minutes by using a 21-channel scalp EEG. In 31 of the patients, EEGs were performed with the additional use of nasopharyngeal or anterior temporal leads. Twenty-two of the patients had been sleep deprived for 24 hours before the EEG, and recordings were obtained during drowsiness or light sleep whenever possible. For all 35 patients, EEGs were obtained during a 2-minute period of hyperventilation and in response to photic stimulation. No sedation was used. The EEGs were interpreted clinically by an experienced neurologist who was aware of the patient's clinical diagnosis.

Without knowledge of the EEG results, we dichotomized patients into two groups: those with psychosensory symptoms (N=15) and those without psychosensory symptoms (N=20). This evaluation was conducted retrospectively on the basis of a chart review of each patient's clinical symptoms as recorded by the admitting psychiatrist. Because of our interest in the relationship between temporal lobe epilepsy and psychiatric disorders (4, 13, 14), considerable information was documented about psychosensory symptoms in our panic disorder patients. The group with psychosensory symptoms commonly complained about symptoms of derealization, depersonalization, visual or auditory perceptual disturbances, or "forced thinking" during panic attacks; these symptoms were either absent or occurred infrequently in the group without psychosensory symptoms. We tested the possible association between EEG abnormalities of any sort and the presence of psychosensory symptoms using a two-

Received July 7, 1988; revision received Sept. 16, 1988; accepted Oct. 7, 1988. From the Unit on Anxiety and Affective Disorders, Biological Psychiatry Branch, NIMH. Address reprint requests to Dr. Uhde, NIMH, Bldg. 10, Rm. 35239, 9000 Rockville Pike, Bethesda, MD 20982.

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TABLE 1. Characteristics of and EEG Findings in 35 Patients With Panic Disorder With or Without Psychosensory Symptoms

Patient and Psychosensory Symptom Group	Age (years)	Sex	Duration of Illness (years)	Nonroutine EEG Type		EEG Result
				Sleep-Deprived	Nasopharyngeal Leads	
No psychosensory symptoms						
1	34	M	10	Yes	Yes	Normal
2	33	M	8	Yes	Yes	Normal
3	34	F	16	Yes	Yes	Normal
4	29	F	4	Yes		Normal
5	31	M	7			Normal
6	31	F	—	Yes	Yes	Normal
7	36	F	2	Yes	Yes	Normal
8	26	F	10	Yes		Normal
9	35	M	6		Yes	Normal
10	32	F	14		Yes	Normal
11	45	M	2	Yes	Yes	Normal ^a
12	42	F	11		Yes	Normal
13	40	F	4	Yes	Yes	Abnormal ^b
14	48	F	8		Yes	Normal
15	38	M	—		Yes	Normal
16	36	F	18			Normal
17	24	M	4		Yes	Normal
18	37	F	6	Yes	Yes	Normal
19	57	F	21		Yes	Normal
20	35	F	9	Yes	Yes	Normal
Psychosensory symptoms						
1	23	M	10	Yes	Yes	Normal
2	26	M	1	Yes	Yes	Normal
3	27	F	14	Yes	Yes	Normal
4	29	F	2	Yes	Yes	Normal
5	43	F	17	Yes	Yes	Abnormal ^c
6	24	F	3		Yes ^d	Normal
7	37	F	16	Yes	Yes	Abnormal ^e
8	30	F	8	Yes	Yes	Abnormal ^f
9	33	F	10	Yes	Yes	Normal
10	46	M	12	Yes	Yes	Normal
11	29	F	4		Yes	Abnormal ^g
12	35	M	18		Yes	Normal
13	24	F	8		Yes	Normal
14	56	F	5	Yes	Yes ^d	Normal
15	39	F	6	Yes	Yes	Normal

^aNo evidence of abnormalities during a panic attack.^bRhythmic midtemporal discharge—intermittent, 6 Hz, 100–140 μ V, bitemporal; clinical significance unknown.^cSharp transient discharges from right nasopharyngeal lead; believed to be artifactual.^dAnterior temporal leads were used.^eBilateral spikes seen anteriorly temporally; clinical significance unknown.^fRhythmic midtemporal discharge during drowsiness—7–9 Hz, 30–40 μ V; clinical significance unknown.^gFrequent bursts of medium- to high-voltage 6–9 Hz activity, mainly over parasagittal regions; clinical significance unknown.

tailed Fisher's exact test at a significance level of $p < 0.05$.

RESULTS

EEG abnormalities of any type were infrequent, occurring in a total of five (14%) of 35 patients (table 1). None of the abnormalities suggested the presence of an epileptiform disturbance but rather were nonspecific in nature. One patient experienced a severe panic attack during his EEG (with nasopharyngeal leads after sleep deprivation), yet his EEG recording was normal. We found no significant association between the presence or absence of EEG abnormalities and the presence or absence of prominent psychosensory symptoms.

DISCUSSION

Our study of 35 medication-free subjects with panic disorder did not uncover any substantial evidence in favor of a high prevalence of EEG abnormalities in patients with panic disorder. Two patients exhibited the EEG pattern referred to as rhythmic midtemporal discharge (a 6/sec spike and wave complex also known as "psychomotor variant") (15), which is probably not unique to panic and is of unknown clinical significance (16–18).

Several difficulties in the diagnosis of complex partial seizures must be addressed before our findings can be interpreted. Patients with complex partial seizures often may have normal EEGs because the epileptic focus may arise from deep within the limbic areas of the

temporal and frontal lobes, areas that are not accessible to standard surface electrodes. The use of sleep deprivation to yield activation and the use of nasopharyngeal monitoring have been used to increase the yield, but the value of these techniques in enhancing sensitivity has been questioned (19). Devinsky et al. (20) recently reported the case of a 13-year-old girl with "fear episodes" whose limbic seizures could only be determined by the use of subdural electrode recordings. Although this is not a technically feasible or desirable approach to diagnosis in most cases, it highlights the technical difficulties encountered in documenting electrical discharges of limbic lobe origin.

Several salient clinical messages emerge from our findings. Given the intrinsic limitations in the usefulness of surface EEG recordings in this situation and the paucity of relevant abnormalities detected, we suggest that an EEG need not be a routine part of the medical evaluation of most patients with panic disorder, a recommendation that we (1) and others (21) have made previously. Those symptoms which indicate a distinct need for EEG evaluation include ones most likely to be differentially associated with partial complex seizures: loss of consciousness, motor automatisms, aphasia, or hallucinations (1, 3, 22). Furthermore, our findings should serve as a reminder that psychosensory symptoms are frequently encountered in the panic syndrome (4). The presence of these psychosensory symptoms does not seem to indicate a greater likelihood of EEG abnormalities or of response to the anticonvulsant carbamazepine (13). Analogous findings have been reported for patients with affective disorder (23) and patients with borderline personality disorder (24).

Even though the presence of psychosensory symptoms does not seem to denote anything atypical, several recent reports (5) suggest that certain other atypical clinical features of panic disorder (such as hostility, irritability, and social withdrawal) may occur in a group of patients who exhibit a good response to anticonvulsants. Although such observations require confirmation in controlled studies, they may be indicative of a subgroup of patients with panic attacks in whom the distinction between epilepsy and pure psychiatric disorder becomes very unclear (6).

In conclusion, given the technical limitations of surface EEG recordings, our findings should not be used to suggest that panic disorder and complex partial seizures do not share a common pathophysiologic mechanism or site of dysfunction. In fact, the striking overlap in psychic, somatic, and autonomic (25, 26) manifestations and the reports of concomitant panic disorder and epilepsy (6, 9, 20) are highly suggestive of an intimate relationship between panic disorder and temporal lobe epilepsy. This hypothesis is also supported by the vast literature on fear or panic-like attacks occurring as a result of temporolimbic stimulation or irritation (8–11, 27). Furthermore, the recent observation that panic attacks may occur spontaneously during non-REM sleep (28) parallels the well-known phenomenon of seizures that arise during these

sleep stages (15) and should draw our attention to the search for mechanisms common to panic disorder and epilepsy.

In addition, recent advances to our technological armamentarium have allowed for more refined approaches to the study of particular brain areas of interest in panic disorder. Intriguing results from positron emission tomography (PET) studies (29) suggest the possibility of an abnormal hemispheric asymmetry in parahippocampal blood flow and oxygen metabolism in patients with panic disorder. Preliminary evidence from brain electrical activity mapping (BEAM) studies in stimulant abusers who develop panic attacks (30) also suggests disturbances in temporal lobe cortical electrical activity. Neither of these studies has identified a specific "hot spot" consistent with an ictal focus. Rather, these studies suggest that a nonepileptiform abnormality in temporolimbic structures may be involved in the pathogenesis of panic. Although ictal activation of these structures may produce panic in some cases, a different pathophysiologic process (such as alterations in excitability, rate, or pattern of neuronal firing) occurring in the same brain areas is more likely to be involved in panic disorder. The delineation, elucidation, and clarification of these hypothetical CNS processes remains as a major challenge to the further understanding of panic disorder.

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Psychosis, Aggression, and Self-Destructive Behavior in Hospitalized Adolescents

Isabelle Delga, M.D., Robert K. Heinssen, Ph.D., Richard C. Fritsch, Ph.D.,
Wells Goodrich, M.D., and Brian T. Yates, Ph.D.

The authors studied the history of aggressive and self-destructive behaviors in psychotic and nonpsychotic hospitalized adolescents (N=137). A multidimensional measure of self- and other-directed aggression was retrospectively applied to each patient's social and developmental history. Nonsignificant gender and diagnostic differences were obtained on ratings of violence and suicide. Broader definitions of internal and external aggression yielded nonsignificant diagnostic differences, but gender differences were observed on both internal and external aggression measures. Females displayed greater internal aggression, and males reported higher external aggression scores. These results, compared to those of other investigators, suggest the importance of social and cultural variables in understanding adolescent psychosis and aggression.

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A study by Inamdar et al. (1) reviewed the psychiatric histories of 51 psychotic adolescents hospitalized at the New York University-Bellevue Medical Center and reported that violent or suicidal behavior characterized the majority of the inpatients. Although this observation is consistent with findings relating psychosis to aggressive and self-destructive behaviors in adult inpatients (2-7), it is inconsistent with other studies of hospitalized adolescents and children (8-10).

While Inamdar et al. (1) correctly pointed out that extreme forms of aggression in adolescents might indicate the presence of a psychotic illness (rather than sociopathy), several methodological problems limit the generalizability of their findings. First, their sample was drawn exclusively from the lowest socioeconomic

classes, where the base rates for aggressive and self-destructive behaviors may be high (11). In addition, the study did not include a nonpsychotic comparison group, which is a necessity for an adequate evaluation. It is, therefore, unclear whether the high rate of violent or suicidal activity reported in the Inamdar et al. study was due primarily to psychopathology, socioeconomic class, or an interaction of psychosis with social and cultural variables. Finally, the definitions of violence and suicide used included only extreme forms of behavior: murder, aggravated assault, and suicidal attempts and gestures. It is possible that less extreme forms of self- and other-directed aggression are more prevalent among adolescents who are not psychotic or who come from higher socioeconomic levels.

The aim of this investigation was to further study the incidence of aggressive and self-destructive behaviors in hospitalized adolescents. In contrast to Inamdar et al. (1), our subjects were drawn from upper socioeconomic classes and contained both psychotic and nonpsychotic patients. Furthermore, subjects were evaluated by multidimensional measures of self- and other-directed aggression. These features made it possible to replicate the methods of Inamdar et al. and to address some of the questions raised by their investigation.

METHOD

Subjects

One hundred forty-five adolescents were admitted to the Adolescent and Child Division of Chestnut Lodge Hospital between July 1975 (the opening date of the unit) and September 1986 (the end of data collection). From this group, 137 patients (79 males, 58 females) had sufficient admission and anamnestic data to be included in this study. Subjects came from predominantly upper socioeconomic brackets (classes I and II [12]) and were of normal intelligence (mean \pm SD IQ = 102 ± 13.5). The mean \pm SD age at admission was 15.7 ± 1.78 years. Most patients (80%, N = 109) had been hospitalized previously, and admission diagnoses ranged from severe personality disturbances to various affective and schizophrenic disorders.

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Each subject's parents were interviewed during the admission process by a psychiatric social worker to obtain a full account of the patient's developmental history. Additional information was obtained from patients' self-reports, school records, and files from previous hospitals. The developmental history derived from this information was found in patients' current hospital charts. Information about each patient's initial clinical presentation was obtained from the administrative psychiatrist's admission note, also found in the patient's current hospital chart. Both documents were necessary for inclusion in this study.

Patients were assigned to psychotic or nonpsychotic categories on the basis of retrospective chart review. This was accomplished by inspecting subjects' medical records for the presence of seven psychotic symptoms described in *DSM-III-R* affective and schizophrenic spectrum disorders (i.e., hallucinations, loose associations, catatonic behavior, emotional turmoil, bizarre delusions, nonbizarre delusions, and grossly inappropriate affect). Four clinical psychology graduate students provided the ratings of psychotic symptoms.

Raters were blind to the hypotheses of the study and were introduced to the scoring task through didactic training sessions. Definitions and examples of each psychotic symptom were first provided by one of the authors (R.C.F.) and raters then practiced applying scoring criteria to several training charts. Ratings were reviewed and scoring discrepancies were resolved before a second set of training charts ($N=4$) were scored. Interrater agreement on the presence or absence of two or more psychotic symptoms was adequate for these records (average kappa statistics $[13]=1.0$). Each graduate student then independently rated approximately 50 medical records. Twenty of these records had been randomly selected for reliability purposes and raters were unaware which charts were checked. The raters demonstrated high levels of agreement (average kappa $=0.82$, range $=0.61$ to 1.00).

Following the criteria proposed by Inamdar et al. (1), we placed patients with two or more psychotic symptoms in the psychotic category. Twenty-four adolescents (18%) were included in this group. The medical records of these patients were further reviewed to determine whether psychotic symptoms were related to the use of illicit drugs. In no instance were psychotic symptoms solely drug-related. Psychotic patients generally had admission diagnoses of schizophrenia, schizophreniform disorder, or brief reactive psychosis, although major affective disorder, borderline and mixed personality disorders, and histrionic personality disorder were also represented. Although small, the proportion of psychotic patients in our sample (18%) is similar to the percentage reported for adolescents hospitalized in comparable private hospital programs, according to a 1987 report from the National Association for Private Psychiatric Hospitals (P.M. Miller, unpublished data).

The remaining patients ($N=113$, 82%) were labeled nonpsychotic. These patients generally received diag-

noses within the conduct disorder, dysthymic disorder, or personality disorder categories. While psychotic patients tended to be slightly older on admission than nonpsychotic patients (mean ages $=16.6$ and 15.5 years; $t=-2.65$, $df=135$, $p=0.004$), no significant differences were found between the groups in gender, socioeconomic class, intelligence, or number of previous hospitalizations.

Procedure

Checklists assessing internally and externally aggressive behaviors were developed following a three-step procedure. First, 76 potential items were drawn from symptom checklists enumerating antisocial, assaultive, self-destructive, and suicidal behaviors (14, 15) and from *DSM-III*, which describes aggressive and self-destructive symptoms present in a variety of psychopathologic conditions. Three members of our research team classified potential items as either externally or internally aggressive. Actions directed toward objects or persons in the environment (e.g., name calling, fighting, fire setting) were classified in the external aggression category. Feelings or actions directed toward the self (e.g., feelings of self-reproach, self-inflicted injuries, suicidal gestures or plans) were classified in the internal aggression category. Only behaviors receiving consistent ratings from all three judges were retained for further analysis. Redundant items were also eliminated from the item pool. These procedures selected 35 items for retention on the internal (13 items) and external (22 items) aggression checklists.

Behaviors sharing similar characteristics were grouped together into separate, nonoverlapping categories. On the Internal Aggression Checklist, for example, the self-reproach category includes feelings of worthlessness and guilt and submissive behavior; the self-injury category includes accident proneness, reckless behavior, drug or alcohol abuse, and self-mutilation; and the suicidal behavior category includes suicidal ideation, plans, gestures, or attempts. On the External Aggression Checklist, the verbal aggression category includes verbal outbursts or threats directed against another and expressions of hatred or dislike; the assaultive behavior category includes threats of physical assault, attacks on another person, and physical torture of animals; and the nonassaultive antisocial behavior category includes stealing, destruction of property, fire setting, truancy, and forgery. (Complete copies of the Internal and External Aggression Checklists are available from Dr. Heinssen.)

Four undergraduate research interns recorded the aggressive behaviors described in patients' medical records. They were unaware of experimental hypotheses and worked independently of the raters assessing psychotic symptoms. The interns recorded the aggressive behaviors reported in a sample set of five developmental histories. Ratings were reviewed with one of the authors (R.K.H.) and scoring discrepancies were resolved. When consensus on the proper application of

TABLE 1. Violent and Suicidal Behavior of Psychotic Adolescents at New York University (NYU)-Bellevue and Chestnut Lodge

Behavior	Study Group Differences ^a				Gender Differences ^b							
	NYU-Bellevue		Chestnut Lodge		NYU-Bellevue				Chestnut Lodge			
	Total (N=51)		Total (N=24)		Male (N=30)		Female (N=21)		Male (N=12)		Female (N=12)	
	N	%	N	%	N	%	N	%	N	%	N	%
Violence	20	39	5	21	25	83 ^c	9	43 ^c	4	33	4	33
Suicide	8	16	5	21	15	50	7	33	4	33	4	33
Violence and suicide	14	27	3	12	13	43 ^d	1	5 ^d	2	17	1	8
No violence or suicide	9	18	11	46	—	—	—	—	—	—	—	—

^aStudy group differences were evaluated with a 2 by 4 chi-square test.

^bGender differences were evaluated by independent 2 by 2 chi-square tests.

^c χ^2 with Yates' correction=7.377, df=1, $p<0.01$.

^d χ^2 with Yates' correction=7.393, df=1, $p<0.01$.

the aggression checklists was achieved, raters began scoring actual data. Each rater scored approximately 37 histories.

Reliability among raters was assessed throughout the scoring phase. Although aware that interrater reliability was being monitored, raters were blind to the timing of the reliability checks. Ratings from 10 developmental histories were used for this assessment. Kappa statistics (13) ranged from 0.88 to 0.92 for internal aggression items and from 0.70 to 0.74 for external aggression items. These results indicated that raters applied the scoring rules for the two aggression scales with adequate consistency.

Data obtained from the aggression checklists were used to classify patients on two dimensions: violence versus suicide and external versus internal aggression. Ratings of violence and suicide were made by using criteria described by Inamdar et al. (1). Adolescents were categorized as violent if they had committed assaultive acts against another person (e.g., sexual assault, physical assault, torture, robbery). Subjects were categorized as suicidal if a serious suicidal threat, gesture, or attempt was reported in the developmental history.

External and internal aggression scores were derived by considering the broad range of aggressive behaviors included in the respective checklists. We recognized that the items on the two aggression measures varied in severity and that the presence of certain behaviors (i.e., physical assaultiveness) suggested greater levels of aggression than others (i.e., verbal threats). Simply summing the constituent behaviors of the checklists could therefore yield invalid assessments of aggression. Thus, it was necessary to estimate each behavior's level of severity so that severe behaviors could be weighted more heavily in patients' aggression scores.

The relative severity of each of the 22 external and 13 internal aggression items was rated independently by nine mental health research professionals on a 7-point scale (1=mild aggression, 7=extreme aggression) to determine each item's aggression weight. External aggression items and internal aggression items were rated and analyzed as two separate sets. Each rater's scores were ipsatized to yield deviation values.

These standardized scores were then averaged across raters to determine the final severity weighting for any given aggression item.

This standardization procedure made the average severity weighting 1.00 for both internal aggression items (range=0.36 to 1.87) and external aggression items (range=0.34 to 1.89). The weighted aggression scores for each patient were then combined to provide summary internal and external aggression scores. The summary scores were used in subsequent analyses.

RESULTS

Comparisons of the Chestnut Lodge and New York University-Bellevue groups are presented in table 1. While Inamdar et al. (1) reported a predominance of violent and suicidal behavior in their psychotic adolescents (82%), this finding was not replicated in the present investigation. An *absence* of violent and suicidal activity characterized almost half (46%) of our psychotic patients. Chi-square analysis revealed that the proportions of violent and suicidal behavior reported for the two groups were significantly different ($N=75$, $\chi^2=8.38$, $df=3$, $p<0.04$).

Gender differences among psychotic adolescents hospitalized at Chestnut Lodge are also reported in table 1. Independent chi-square tests replicated the analyses of Inamdar et al. and evaluated gender differences in three categories of violent and suicidal behavior. For these analyses, the violence category included all patients with a history of violence, regardless of the presence or absence of suicidal activity. Similarly, the suicidal category included all patients with a history of suicidal behavior, whether or not violence was ever present in the patient's history. Contrary to the findings of Inamdar et al. (1), no significant differences between male and female patients were observed on these dimensions.

As reported in table 2, no significant differences were observed between our psychotic and nonpsychotic adolescents in the three categories of violence and suicide. Furthermore, the proportion of males and

TABLE 2. Violent and Suicidal Behavior of Psychotic and Nonpsychotic Adolescents at Chestnut Lodge

Behavior	Psychotic Patients (N=24)		Nonpsychotic Patients (N=113)		Male Patients				Female Patients			
					Psychotic (N=12)		Nonpsychotic (N=67)		Psychotic (N=12)		Nonpsychotic (N=46)	
	N	%	N	%	N	%	N	%	N	%	N	%
Violence	8	33	46	41	4	33	35	52	4	33	11	24
Suicide	8	33	34	30	4	33	14	21	4	33	20	44
Violence and suicide	3	13	12	11	2	17	8	12	1	8	4	9

females in the violent, suicidal, and violent and suicidal categories did not differ significantly between the diagnostic groups (table 2).

Results from the 2 by 2 analyses of variance (gender by diagnostic group) performed on external and internal aggression scores revealed nonsignificant differences between the diagnostic groups. Significant gender differences were observed, however, on both the internal ($F=6.54$, $df=1$, 133, $p<0.01$) and external ($F=9.51$, $df=1$, 133, $p<0.002$) aggression measures. Female patients reported higher internal aggression scores ($\text{mean}\pm\text{SD}=2.3\pm1.7$) than males ($\text{mean}\pm\text{SD}=1.6\pm1.4$), and boys had higher external aggression scores (4.9 ± 2.3) than girls (3.7 ± 2.4). A significant interaction between the gender and diagnostic variables was observed on the external aggression scale ($F=5.25$, $df=1$, 133, $p<0.02$). Post hoc analyses (Scheffé's procedure) indicated that nonpsychotic males received significantly higher external aggression scores than nonpsychotic females (5.2 ± 2.2 versus 3.4 ± 2.4 ; $F=5.95$, $df=3$, 133, $p<0.05$).

DISCUSSION

Significant differences were found between the Bellevue and Chestnut Lodge groups. Unlike the Bellevue cohort, a history of violence was not a defining characteristic of the psychotic adolescents at Chestnut Lodge. This finding contradicts Inamdar et al.'s conclusion that "violent behavior or suicidal behavior is a common behavioral manifestation of psychosis in adolescents" (1, p. 935) and suggests that psychosis and violence are not linked in all adolescent psychiatric populations.

Since the Bellevue subjects were drawn from an urban group with low socioeconomic status and Chestnut Lodge patients came generally from suburban, high socioeconomic backgrounds, it is possible that variables associated with socioeconomic status mediate the expression of psychosis and violence in adolescent patients. This hypothesis will require further testing, however, since both the Bellevue and Chestnut Lodge groups are highly atypical on the socioeconomic dimension. Future investigations will need to study subjects from wider bands of socioeconomic class and psychopathology to accurately assess the relationship between psychosis and violence. Nonetheless, our failure to replicate the findings of Inamdar et

al. (1) does not invalidate their important point that violence may be a manifestation of psychosis for certain adolescents and is not necessarily an indicator of sociopathic adjustment.

Our failure to find gender differences for extreme forms of violent behavior was surprising, since expected differences (i.e., males with higher external aggression scores) did emerge when we used broader definitions of aggressive behavior. Two alternative explanations may account for these results. First, the absence of gender differences for extreme forms of violence may reflect the infrequent occurrence of such behaviors in higher socioeconomic groups. A more likely possibility is that private facilities, which have a measure of control over the admission process, may refuse to admit violent male patients. Violent female patients may be admitted, however, if the institution believes that females can be contained by the milieu. Thus, the inconsistency of gender differences for violent and suicidal behaviors in the Bellevue and Chestnut Lodge groups may reflect different admission policies for public and private psychiatric institutions.

Other results reported here highlight the importance of including relevant control groups in psychiatric research. No diagnostic differences were observed in the prevalence of violent and suicidal behaviors, indicating that our psychotic adolescents were no more prone to violence or suicide than their nonpsychotic counterparts. These nonsignificant results were replicated when broader definitions of aggression were employed. Furthermore, in analyzing the interaction of gender, diagnosis, and external aggression, we found that gender-linked differences for external aggression were present only within the nonpsychotic cohort. While the implications drawn from Inamdar et al. (1) were for heightened vigilance to prevent further aggression in psychotic adolescents, our results suggest that these concerns are equally relevant for the evaluation and treatment of nonpsychotic adolescents.

In conclusion, we feel that our findings have important practical implications. These data suggest that mental health and juvenile justice workers should consider a variety of factors when making dispositional decisions for adolescents with histories of violent or psychotic behavior. The possibility that violence is linked to a psychotic illness should be considered for adolescents from lower socioeconomic groups. Similarly, adolescents with violent personality disorders or violent antisocial disorders should be differentiated

from violent psychotic adolescents in terms of treatment planning. For all psychotic adolescents, regardless of socioeconomic status, violent behavior should be examined for intrapsychic, familial, and subcultural determinants. Treatment planning for these adolescents should focus on containing and eventually resolving the mental disorganization that underlies the violent behavior.

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High Prevalence of Visual Hallucinations in Research Subjects With Chronic Schizophrenia

H. Stefan Bracha, M.D., Owen M. Wolkowitz, M.D.,
James B. Lohr, M.D., Craig N. Karson, M.D., and Llewellyn B. Bigelow, M.D.

The authors examined the prevalence of visual hallucinations in severely ill hospitalized research subjects with carefully diagnosed chronic schizophrenia and found it to be high. A chart review of 100 discharged subjects revealed documentation of visual hallucinations in 32%, and a prospective examination of 43 additional subjects revealed a history of visual hallucinations in 56% (N=24). Also, the fact that in 43% of the patients with visual hallucinations the history of visual hallucinations was first documented during the research ward work-up suggests that clinicians frequently do not inquire about visual hallucinations in patients with chronic schizophrenia.

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Visual hallucinations, which are typical of drug-induced and metabolic psychoses, have been thought to be infrequent in schizophrenia (1-3). This notion was probably based on a study by Goldberg et al. in 1965 (4), which reported visual hallucinations in 18% of 270 DSM-I schizophrenic patients from the National Institute of Mental Health (NIMH) collaborative study of phenothiazine treatment. Other reports of visual hallucinations in patients with schizophrenia (5-8) indicate that they may be present in 30%-62% of schizophrenic patients. Some researchers (7, 8), however, consider the high prevalence of visual hallucinations in their subjects to be representative of "local cultural anomalies" and possibly not relevant to all patients with schizophrenia. Therefore, we decided to examine the prevalence of visual hallucinations in severely ill chronic schizophrenic research subjects in

whom drug abuse and metabolic psychoses had been carefully ruled out. Because Goldberg (9) has suggested that visual hallucinations are a marker of neuroleptic resistance among schizophrenic patients, we compared the scores of the NIMH version of the Brief Psychiatric Rating Scale (NIMH-BPRS) in patients with and without visual hallucinations after a 6-week drug-free period and after 6 weeks of treatment with haloperidol.

METHOD

We conducted a retrospective study of 106 research volunteers who had been admitted over a 5-year period to the inpatient research wards of NIMH (at St. Elizabeths Hospital, Washington, D.C., and at the Clinical Center, Bethesda, Md.). All met DSM-III criteria for chronic schizophrenia and had been inpatients for at least 1 month (eight also met criteria for affective illness and were diagnosed as having schizoaffective disorder). Their extensive NIMH charts and predischarge summaries were reviewed by one of us (H.S.B., O.M.W.) for documentation of visual hallucinations. Of the 106 patients, six were excluded from the final sample because the treating psychiatrists suspected drugs to be the cause of their visual hallucinations.

Because drug abuse, alcohol withdrawal, and metabolic psychoses were suspected as the cause for such "atypical" hallucinatory symptoms among these 106 schizophrenic patients, we prospectively examined all the patients consecutively admitted to the same NIMH research services over a 1½-year period (N=44). These patients met DSM-III criteria for chronic schizophrenia by consensus of three research psychiatrists. None of the patients met criteria for current substance abuse, and there was no record of alcohol dependence or any drug abuse in the 2 years before admission. All had undergone the standard NIMH metabolic and endocrine work-up, toxicology screen, EEG, and a CT or magnetic resonance imaging (MRI) scan. We asked the staff psychiatrists of the four NIMH schizophrenia research wards to refer to us research subjects with schizophrenia who had unequivocal visual hallucinations. They were asked to take extreme care to exclude illusions, perceptual distortions, and visual hallucina-

Received June 12, 1987; revision received June 13, 1988; accepted Oct. 18, 1988. From the Intramural Research Program, NIMH, Neuropsychiatry Branch, Washington, DC, and Clinical Neuroscience Branch, Bethesda, Md. Address reprint requests to Dr. Bracha, Psychiatry Service, VA Medical Center (116A/NLR), North Little Rock, AR 72114.

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tory experiences that could be related to concurrent drug abuse or use of drugs with anticholinergic effects. The patients referred were reexamined by one of us while they were taking antipsychotics and while they were drug free to rule out the possibility of anticholinergic drug-induced visual hallucinations. Thus, each patient was examined by one additional psychiatrist for the presence or absence of visual hallucinations. One patient was excluded because his visual phenomena could have been secondary to pigmentary retinopathy. The criteria for visual hallucinations were taken from the *DSM-III* glossary of technical terms: "A sensory perception without external stimulation of the relevant sensory organ . . . involving formed images, such as people, or unformed images such as flashes of light . . ."

To determine if patients with visual hallucinations are more resistant to neuroleptics, as suggested by Goldberg (9), we also compared NIMH-BPRS scores (range, 0–6) and medication-induced percent change in NIMH-BPRS scores in 39 of the 43 patients (20 with and 19 without visual hallucinations) after a 6-week drug-free period and after 6 weeks of treatment with haloperidol at a dose of 0.4 mg/kg of body weight per day.

RESULTS

The retrospective chart review of 100 patients discharged with a diagnosis of schizophrenia revealed clear documentation of past or current visual hallucinations in 32% of the patients. Of the 100 patients, 4% had had tactile hallucinations, none had had olfactory hallucinations, and 84% had had auditory hallucinations.

Of 43 consecutively admitted patients in our prospective study who were reexamined for the presence or absence of visual hallucinations as part of schizophrenia, 24 (56%) reported unequivocal histories of past or present chronic visual hallucinations that could not be explained by anything other than schizophrenia. Of the 43 patients, 42 (98%) reported a history of auditory hallucinations.

Of the 32 patients in our retrospective study, most described having visual hallucinations in black and white, a few in white only, and some in colors. Some of the more common visual hallucinations were faces, lights, religious manifestations (God, church, Christ, the devil), and people (including friends and relatives).

Fisher's exact test revealed that more patients in the prospective study had visual hallucinations than in the retrospective study ($p=0.01$). In 112 of the 143 patients in both studies, we were able to determine when the presence or absence of visual hallucinations was first clinically documented. In 24 (43%) of the 56 visually hallucinating patients (32 in the retrospective study, 24 in the prospective study), the histories of non-drug-related visual hallucinations were first documented during the research ward work-up.

Among the 143 patients in both studies, we were

able to determine a clear diagnosis of a *DSM-III* subtype of schizophrenia or schizoaffective disorder for 88 patients. Of the 25 patients with paranoid schizophrenia, five (20%) had visual hallucinations. A total of 63 patients had a nonparanoid diagnosis, and 20 (32%) of them had visual hallucinations. The nonparanoid subtypes of schizophrenia included undifferentiated ($N=47$), disorganized ($N=3$), and catatonic ($N=5$); visual hallucinations were present in 16 (34%), one, and no patients, respectively, and in three of the eight patients with schizoaffective disorder. Fisher's exact test revealed no significant differences between paranoid and nonparanoid patients with respect to visual hallucinations.

A Wilcoxon test with Bonferroni correction for multiple tests revealed no significant differences between mean \pm SD scores on the NIMH-BPRS or neuroleptic-induced percent change in these scores for 20 patients with and 19 patients without visual hallucinations. The scores were 1.6 ± 0.6 and 2.1 ± 0.7 , respectively, at the end of the 6-week drug-free period and 1.3 ± 0.6 and 1.5 ± 0.7 , respectively, after 6 weeks of treatment with 4 mg/kg of haloperidol, and the percent change due to neuroleptics was $14\% \pm 32\%$ and $27\% \pm 25\%$, respectively.

DISCUSSION

Although we concur with Roberts (10) that visual hallucinations in schizophrenia "are usually associated with auditory hallucinations, delusions and thought disorder," we found the prevalence of visual hallucinations in 143 patients with *DSM-III* chronic schizophrenia to be considerably higher than previously assumed (1–4). The prevalences of 32% and 56% in the two independent samples studied are consistent with the findings of four other studies (5–8). As expected, practically all of the schizophrenic patients with visual hallucinations in our prospective study also experienced auditory hallucinations. Surprisingly, in 24 (43%) of the 56 patients in both studies who had visual hallucinations, a history of non-drug-related visual hallucinations was first documented during the research ward work-up, a finding which suggests that psychiatrists do not always inquire about visual hallucinations in patients with chronic schizophrenia.

Several factors could account for a high prevalence of visual hallucinations on NIMH research wards. The high staff to patient ratio allows intensive observation and documentation of each patient's symptoms. On average, patients are evaluated for more than a year. Also, there is an extensive period of placebo substitution for neuroleptic medications. Many of these drug-withdrawn patients were observed behaving in a manner that suggested the presence of visual hallucinations and often acknowledged them at the time; however, only improvement after neuroleptic treatment enabled some patients to acknowledge that they had experienced visual hallucinations.

The chart review method may have also influenced our results and therefore may be of limited value. For example, because we were looking for visual hallucinations, the prevalence of 32% in our retrospective survey may have been artificially high as a result of rater bias. However, our prospective study, in which we asked staff psychiatrists of the four NIMH schizophrenia research wards to identify schizophrenic research subjects who had unequivocal non-drug-related visual hallucinations, affirms the high prevalence of visual hallucinations in hospitalized chronic schizophrenic patients. None of the patients in our prospective study met criteria for past or present substance abuse. In fact, throughout their illness these severely ill chronic patients rarely improved enough to be left unsupervised or to be given a pass without a family escort. It is unlikely that any episodes of visual hallucinations reported here were secondary to drug use or alcohol withdrawal.

One criterion for admission to the NIMH research programs is the presence of active symptoms that are relatively refractory to conventional treatment. The high prevalence of visual hallucinations that we found may reflect more severe symptoms than might exist in a random sample of patients with chronic schizophrenia in a general hospital. Our survey, however, strongly suggests that the high prevalence of visual hallucinations reported in earlier studies of schizophrenia (5–8) is genuine and not a result of lax diagnostic criteria or incomplete diagnostic work-up.

The comparison of the mean NIMH-BPRS scores of our patients does not support speculations (9) that visual hallucinations are a marker of neuroleptic resistance. In fact, the percent change in scores due to neuroleptics among schizophrenic patients with visual hallucinations was slightly greater. This finding also does not support the notion that our schizophrenic patients with visual hallucinations are atypical.

In 1965 Goldberg et al. (4) reported that among 270 patients from the phenothiazine treatment collaborative study, 18% had visual hallucinations. Our study supports the findings of four more recent research studies. Small et al. (5) found a 30% prevalence of visual hallucinations among hospitalized, *DSM-I* chronic schizophrenic inpatients. Phillipson and Harris (6), in a questionnaire study, reported a prevalence of 59% among 73 British outpatients with schizophrenia. Ndeti and Singh (8) reported a prevalence of 43% among 51 inpatients with schizophrenia from Kenya given the Present State Examination and diagnosed according to criteria of the New Haven Schizophrenia Index. Zarroug (7) noted a prevalence of 62% among

69 consecutively admitted patients with schizophrenia from Saudi Arabia. Thus, the prevalences we found support the notion of few (if any) transcultural differences in the clinical picture of schizophrenia.

As the criteria for schizophrenia have gradually narrowed from earlier studies to more recent studies (11), the percent of schizophrenic patients with visual hallucinations has increased (5–8). The low prevalence of visual hallucinations reported in early U.S. studies may have resulted from the inclusion of affective disorder patients. Winokur (12) reported that while the prevalence of delusions was approximately 50% in both bipolar and unipolar hospitalized patients, the prevalence of visual hallucinations in the same patients was 9% in those with bipolar disorder and 1% in those with unipolar disorder. Therefore, although the presence of delusions is not helpful in differentiating affective from schizophrenic disorders (13), our results and those of Winokur (12) suggest that once exogenous and metabolic psychoses are ruled out, visual hallucinations in a chronic psychiatric patient are relatively specific to the syndrome of schizophrenia.

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Benzodiazepine Dependence and Withdrawal in Elderly Patients

Edward Schweizer, M.D., W. George Case, M.D., and Karl Rickels, M.D.

Severity of withdrawal symptoms and clinical outcome were compared in 19 elderly and 22 younger benzodiazepine-dependent patients matched for benzodiazepine half-life, dosage, and duration of treatment. During gradual taper of benzodiazepine doses, the elderly patients showed significantly less severe withdrawal symptoms on several clinical measures and a comparably favorable outcome. Approximately half of each group remained benzodiazepine free for at least 4 weeks. Both groups of patients tolerated drug discontinuation without serious consequences such as seizures or psychosis. Tapered benzodiazepine withdrawal did not appear to be more risky for the elderly group than for the younger patients.

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The elderly receive a great deal of benzodiazepine treatment. One survey (1) reported that 26% of prescriptions for benzodiazepine anxiolytics and 40% of prescriptions for benzodiazepine hypnotics had been written for patients 65 years of age or older. Another survey (2) found that 33% of long-term daily benzodiazepine users were elderly.

Despite the high prevalence of chronic benzodiazepine use, benzodiazepine withdrawal in the elderly has not been well studied. Preliminary reports, however, have suggested that benzodiazepine discontinuation may more commonly result in a serious withdrawal syndrome in elderly patients than in younger patients (3). This paper reports on a controlled study that compared the severity of withdrawal effects and the clinical outcome in a group of elderly patients and a group of younger patients undergoing gradual withdrawal from benzodiazepines.

Received May 23, 1988; revision received Oct. 24, 1988; accepted Nov. 10, 1988. From the Psychopharmacology Research Unit, Department of Psychiatry, University of Pennsylvania. Address reprint requests to Dr. Rickels, 203 Piersol Bldg., University Hospital, 34th and Spruce Streets, Philadelphia, PA 19104.

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METHOD

Nineteen elderly outpatients (age ≥ 60 years) and 22 younger outpatients (age < 55 years) were drawn from a larger group of 110 patients who had been taking benzodiazepines daily for a minimum of 1 year and who had been recruited into a benzodiazepine discontinuation program by physician referral, self-referral, or notices in the local media. The elderly subjects, 42% (N=8) of whom were male, had a mean \pm SD age of 66.4 ± 5.1 years (range=60-80 years); the younger patients, 45% (N=10) of whom were male, had a mean age of 34.4 ± 6.8 years (range=25-52 years). Eighty-six percent (N=35) of the 41 patients had at least a high school education.

The two groups were matched for daily benzodiazepine dosage, duration of benzodiazepine treatment, and benzodiazepine half-life. Six elderly and seven younger patients were taking long-half-life benzodiazepines (diazepam and clorazepate). Thirteen elderly and 15 younger patients were taking short-half-life benzodiazepines (lorazepam and alprazolam). Written informed consent was obtained from all patients. The drug discontinuation protocol consisted of an initial psychiatric evaluation, including the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (4) and an intensive history of past illness and drug use; a physical examination, an ECG, and laboratory testing; and administration of a variety of psychological measures, including the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, the 80-item Hopkins Symptom Checklist (5), from which was derived the Covi withdrawal cluster (6), and a 37-item withdrawal checklist scored by a physician. In addition, personality characteristics were assessed by means of the Eysenck Personality Inventory (7) and the MMPI (8).

The percentages of the elderly and younger patients, respectively, who received current DSM-III diagnoses were as follows: major depression, 32% and 14%; other affective illness, 11% and 0%; generalized anxiety disorder, 32% and 41%; panic disorder, 0% and 22%; no diagnosis, 26% and 23%. There was a trend for more depression, but less panic disorder, in the elderly than in the younger patients ($\chi^2=7.69$, $df=3$, $p<0.10$).

All of the patients underwent gradual withdrawal,

TABLE 1. Treatment History and Scores on Psychological Measures of 19 Elderly and 22 Younger Patients Undergoing Benzodiazepine Withdrawal

Measure	Elderly Patients (≥ 60 years of age)		Younger Patients (<55 years of age)	
	Mean	SD	Mean	SD
Benzodiazepine dose (in diazepam equivalents) (mg)	16.4	12.5	16.6	12.8
Length of benzodiazepine treatment (cumulative months)	78.0	64.0	80.0	66.0
Hamilton anxiety score	16.4	8.6	17.5	10.1
Hamilton depression score	15.1	8.0	14.1	9.4
Eysenck neuroticism score	14.2	5.09	15.4	5.7
MMPI total score ^a	66.7	11.0	69.5	10.4

^aMean of nine standard scales, excluding Male-Female scale.

which consisted of an open-label 25% per week reduction of their daily benzodiazepine doses, if this could be tolerated. The patients were evaluated at weekly intervals. Their compliance with the tapered dosage was confirmed by weekly determinations of benzodiazepine plasma levels.

Statistical significance of the results was assessed by chi-square tests (with Yates' correction where appropriate) for dichotomous variables and two-tailed Student's *t* tests for continuous variables.

RESULTS

Table 1 summarizes the benzodiazepine treatment history and scores on prewithdrawal clinical measures for each group. There were no significant differences between the two age groups in treatment history, psychopathology, or personality measures.

Withdrawal of drugs at the 25% per week rate was generally well tolerated, although 33% (*N*=6) of the elderly and 50% (*N*=11) of the younger patients required a slowing of this rate. The mean \pm SD number of days to successful withdrawal was 41 ± 29 for the elderly (*N*=12) and 39 ± 15 for the younger (*N*=14) patients. There were no reports of serious medical or psychological sequelae in either group in the wake of discontinuing chronic use of benzodiazepines. No seizures or psychotic reactions were observed.

The effects of gradual tapering of benzodiazepine doses on the patients' clinical symptoms are indicated by the differences between the prewithdrawal baseline scores and the peak scores during withdrawal on the various psychological measures. The change score on the Hopkins checklist withdrawal cluster was significantly worse for the younger group (mean \pm SD = 0.55 ± 0.5 for the younger patients and 0.05 ± 0.5 for the older patients; $t=3.24$, *df*=39, $p<0.01$). The same was true for the change score on the Hamilton anxiety scale (8.5 ± 6.8 for the younger patients and 4.3 ± 5.9 for the older patients; $t=2.18$, *df*=39, $p<0.05$). The change score on the withdrawal checklist rated by a

physician showed a trend toward worse status in the younger patients (17.5 ± 11.9 for the younger group and 10.3 ± 13.0 for the older group; $t=1.89$, *df*=39, $p<0.07$). Overall, the elderly patients suffered from a significantly less severe withdrawal syndrome than their younger counterparts, despite comparable benzodiazepine dosage and duration of chronic benzodiazepine treatment. The younger patients also reported significantly more new symptoms on the withdrawal checklist than did the elderly (mean \pm SD = 8.1 ± 5.3 and 4.8 ± 5.5 , respectively; $t=2.1$, *df*=39, $p<0.05$). If a withdrawal syndrome is defined as the occurrence in any patient of more than five new symptoms, then 68% (*N*=15) of the younger patients and 47% (*N*=9) of the elderly patients experienced a withdrawal syndrome. While this difference was not statistically significant, it was still consistent with the clinical picture of less severe effects of withdrawal in the elderly than in the younger patients.

One week after the last 25% dose reduction (i.e., when patients had been free of benzodiazepines for 1 week), four elderly and three younger patients withdrawn from long-half-life benzodiazepines still had diazepam plus desmethyldiazepam in their plasma (mean \pm SD = 152 ± 119 and 97 ± 49 ng/ml, respectively). In contrast, of the patients withdrawn from short-half-life benzodiazepines, only the elderly patients (*N*=6), and none of the younger patients (*N*=8), had measurable plasma levels of benzodiazepine (for the elderly, mean \pm SD = 5.6 ± 8.1 ng/ml). This difference was statistically significant (Fisher's exact test, $p<0.05$).

There was no significant difference between the elderly and younger groups of patients in benzodiazepine-free status 4 weeks after discontinuation of benzodiazepines ($\chi^2=0.03$, *df*=39, *n.s.*). Fifty percent (*N*=11) of the younger patients and 47% (*N*=9) of the elderly remained free of benzodiazepines for at least 4 weeks.

DISCUSSION

The results demonstrate that elderly patients tolerate gradual benzodiazepine taper as well as, if not better than, their younger counterparts. The physician-rated scales, such as the withdrawal checklist and the Hamilton anxiety scale, and the patient-rated Hopkins Symptom Checklist withdrawal cluster were consistent in showing that the elderly patients' withdrawal experience was less severe than that of the younger patients. These findings are reassuring and are in contrast to the frequently expressed clinical opinion that one should be cautious when withdrawing elderly patients from benzodiazepine use (9). This attenuated withdrawal experience was not different enough, however, to translate into a difference in clinical outcome 4 weeks after discontinuation of benzodiazepines; approximately 50% of both the elderly and the younger

groups were free of benzodiazepines for at least 4 weeks.

It is possible that the results would have been different for both age groups if the patients who were unable to tolerate withdrawal had not been allowed to restart their benzodiazepines, but since the study involved outpatients, such stringent guidelines were precluded. In addition, the relatively small sample size dictates that the results of the study be interpreted with caution.

We can only speculate about the reason for the apparent attenuation of withdrawal symptoms in the elderly. Factors that have been previously reported to contribute to the severity of these symptoms—daily dose of the benzodiazepine, duration of benzodiazepine treatment, type of taper, half-life of the benzodiazepine, baseline psychopathology (as measured by the Hamilton anxiety and depression scales), and level of personality dysfunction (as measured by the Eysenck inventory and the MMPI)—were similar in the two groups in this study.

The elderly in the study suffered more from depression and less from panic than the younger control patients. It is possible that the presence of panic disorder in the younger patients constituted a risk factor which contributed to the somewhat greater severity of withdrawal symptoms we observed in them.

Another possible explanation may lie in the rate of decline in plasma levels of benzodiazepine. Although the daily benzodiazepine dose was comparable for both groups, clearance of benzodiazepines from plasma has been shown to be slower for elderly patients (10). This somewhat slower rate of clearance may thus partially explain why our elderly patients reported a less severe withdrawal syndrome.

A final speculative explanation for our results is the following. Cowen and Nutt (11) have hypothesized that the benzodiazepine withdrawal syndrome is in part the result of a drug-discontinuation-induced overactivity of noradrenergic, serotonergic, and cholinergic systems that have been tonically inhibited by chronic benzodiazepine administration. It is possible that the functional capacity of these systems is reduced in the

elderly (12). As a result, benzodiazepine discontinuation might result in less "overdrive."

In summary, gradual taper of chronically administered benzodiazepines given in therapeutic doses is at least as well tolerated by elderly as by younger patients. It appears to result in a less severe withdrawal syndrome than that which is observed in younger benzodiazepine-dependent patients. Ability to maintain a benzodiazepine-free state for the short term (≥ 4 weeks) was similar for both age groups. Thus, age need not be an important consideration when planning a tapered benzodiazepine discontinuation.

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A Magnetic Resonance Imaging Study of Autism: Normal Fourth Ventricle Size and Absence of Pathology

H. Jordan Garber, M.D., Edward R. Ritvo, M.D., Lee C. Chiu, M.D.,
Virginia J. Griswold, M.D., Alona Kashanian, B.S.,
B.J. Freeman, Ph.D., and William H. Oldendorf, M.D.

Magnetic resonance imaging did not diagnose neuropathology in 15 autistic patients. Measurements of the midsagittal area and volume of the fourth ventricle did not differ between these patients and matched control subjects.

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Despite its uncertain etiology and pathophysiology, autism is a well-characterized clinical syndrome (1). Theories suggesting abnormal CNS development in autism are supported by several lines of evidence, including post-mortem findings of multiple areas of cellular abnormality (2) and lower numbers of cerebellar Purkinje cells (3). Recent studies of autistic patients in which magnetic resonance imaging (MRI) was used have described various cerebral abnormalities (4), enlargement of the fourth ventricle (5), and hypoplasia of the cerebellar vermis (6), particularly lobules VI and VII (declive and folium-tuber) (7). Computed tomography (CT) has yielded conflicting results:

some investigators have reported ventricular enlargement and focal abnormalities in some patients (8), but others have reported no differences between patients and control subjects (9).

Since MRI provides better visualization of the posterior fossa than CT, we undertook an MRI study of autistic patients and matched normal control subjects.

METHOD

From the clinical population of autistic patients at UCLA (previously diagnosed by E.R.R. according to DSM-III criteria), 15 patients who were able to complete the MRI procedures were selected. There were 11 males and four females, aged 5-19 years (mean \pm SD = 11.6 ± 4.1 years). The group of patients included a 6-year-old boy with microcephaly whose mother had cytomegalovirus infection, a 12-year-old girl who had had neonatal anoxia and seizures, and three children with abnormal EEG patterns (one had persistent seizures). The patients were grouped according to IQ (WISC-R), as suggested by Freeman et al. (10): high intelligence (verbal IQ > 70 and performance IQ > 70), medium intelligence (verbal < 70 , performance > 70), and low intelligence (verbal < 70 , performance < 70). This resulted in five patients per IQ group.

The control subjects were 15 normal children matched to the patients on a case-control basis for age ($\pm 10\%$ by years), sex, and race. Recruited by advertisement and personal contacts, they were free of medical illness and personal and family histories of neurologic or psychiatric illness, including mental retardation.

Parents' informed consent and subjects' assent were obtained. High-resolution MRI studies were performed with a Picker Vista 1.5-tesla magnetic reso-

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nance imager (25-cm field of view, number of signals averaged=2, 256 gradient steps, contiguous slices), using T₂-weighted sequences (repetition time [TR]=2000 msec, echo times [TE]=40 and 80 msec) in axial orientation (eight slices, 10 mm thick) and T₁-weighted sequences (TR=800 msec, TE=26 msec) in sagittal orientation (12 slices, 5 mm thick) and coronal orientation (14 slices, 8 mm thick). Positioning of the midsagittal MRI section was standardized by alignment with the apex of the fourth ventricle and the third ventricle as seen on the coronal pilot scan of each subject. Thiopental, 20 mg/kg, was given by rectum, without complication, to eight of the autistic subjects for sedation.

MRI results were evaluated by two radiologists who did not know which subjects were patients and which were control subjects. CSF spaces of the fourth ventricle were identified from the original imaging data with fourfold magnification of sagittal views on an MRI video console. Rostral and caudal boundaries of the fourth ventricle were defined by margins of the pons. A high-pass filter (Avion Division, Picker International, Cleveland, Ohio) with window settings for a constant range of CSF intensities and computerized cursor tracking gave measurements that included only areas of CSF within the fourth ventricle. Measurements were made for midsagittal and other relevant sagittal sections by two blind raters. Repeated measurements showed intrarater correlations greater than 0.95; the interrater correlation for area measurements was 0.92. For each subject, the total volume of the fourth ventricle was calculated by summing all relevant CSF areas, multiplying by slice thickness (0.5 mm), and averaging the results from the two raters. Results were analyzed for age effects by Spearman rank-correlation coefficients and for group comparisons by Mann-Whitney U tests.

RESULTS

Radiologic evaluation of MRI results did not identify definitive neuropathology in any subject. In the 30 MRI studies, three abnormalities of uncertain significance were noted: a smaller than expected cerebellar vermis in a normal control subject (male, aged 13); smaller than expected cranial size in the autistic subject (male, aged 6) whose mother had cytomegalovirus infection; and two minimal foci of prolonged T₂ in the left frontal white matter of an autistic subject (female, aged 5) with an abnormal EEG. No patients or control subjects showed ventricular enlargement, and no gross abnormalities were apparent in the cerebella, including the vermis, of the autistic patients.

Group means were not significantly different for midsagittal areas (for patients, 0.89 ± 0.20 cm²; for control subjects, 0.96 ± 0.17 cm²; $U=88.5$, $df=28$, $p<0.32$) or fourth ventricle volume (for patients, 0.96 ± 0.25 cm³; for control subjects, 1.02 ± 0.22 cm³; $U=96.5$, $df=28$, $p<0.51$). No differences in area or

volume were found between the patient groups based on IQ or between the autistic patients grouped by IQ or sex and their matched case-control groups.

Midsagittal area correlated strongly with total fourth ventricle volume in the control subjects ($r=0.83$, $df=13$, $p<0.0001$) and in the patients ($r=0.65$, $df=13$, $p<0.009$). Age was not significantly correlated with midsagittal area in the patients ($r=0.30$, $df=13$, $p<0.28$) or in the control subjects ($r=0.43$, $df=13$, $p<0.11$). Although increasing age was significantly correlated with greater volume of the fourth ventricle in the patients ($r=0.56$, $df=13$, $p<0.03$) but not in the control subjects ($r=0.39$, $df=13$, $p<0.15$), the difference between the correlations was not significant.

DISCUSSION

Our MRI results agree with CT studies that have found no radiologic abnormalities uniquely associated with autism (9). Nonspecific MRI findings occurred in two autistic patients who had other evidence of organicity. Although maternal infection with cytomegalovirus has been found in association with autism, no causal relationship has been established (1). Foci of prolonged T₂ in white matter suggest a prior cortical insult, but the relation of such events to the development of autism and/or EEG abnormalities is uncertain. Courchesne et al. (6) reported a small vermis in one autistic patient; this was also noted in one of our control subjects. It does not indicate a diagnosis of autism. Gaffney and Tsai (4) reported a variety of MRI abnormalities in a small group of autistic patients, many of whom had unusual histories and evidence of other neurologic disease. Although MRI cannot establish the diagnosis of autism, MRI may be clinically useful in the evaluation of some autistic patients when other CNS diseases or abnormalities are suspected (1).

In our sample and in Gaffney and Tsai's sample (4), several autistic patients with abnormal EEG patterns and seizures had normal MRI findings. While obvious neuropathology may be present and relevant, disturbances in neural development underlying the autistic syndrome (and related seizure disorders) may be too subtle to appear as structural pathology on MRI.

Our failure to confirm MRI studies that have found a small cerebellar vermis (6) and a greater midsagittal area of the fourth ventricle (5) may have resulted from our use of normal control subjects, one MRI technique for all subjects, and standardized midline positioning for contiguous slices. In other studies, control data were primarily from "radiologically normal" results in patients referred for MRI for reasons other than autism. The divergence of results may also reflect the heterogeneity of autistic patients: our autistic group included fewer patients with significant medical histories and more with lower IQ than the group studied by Gaffney et al. (4, 5). Our autistic patients were much younger than those studied by Courchesne et al. (7), and comparison of results is limited because we have

not yet measured the area of the cerebellum or vermis lobules.

We found that greater volume of the fourth ventricle correlated with age in the autistic group but not in the control group. However, because of the small sample sizes and a nonzero correlation for the control subjects, these coefficients did not support a significant difference between groups. Further MRI studies of autism with larger samples are needed to investigate possible neuromaturational disturbances involving the brainstem and/or cerebellum.

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Seasonal Cocaine Abuse

Sally L. Satel, M.D., and Frank H. Gawin, M.D.

The authors describe two patients with seasonal affective disorder characterized by fluctuations in cocaine craving that paralleled seasonal dysphoria. This extends the range of axis I disorders associated with cocaine self-administration.

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We report here the cases of two patients whose episodes of cocaine abuse or craving were triggered by the depressed phase of seasonal affective disorder (1, 2). Self-medication for axis I psychopathology with drugs of abuse has been reported for several disorders, including generalized anxiety, panic disorder, and unipolar and bipolar depression (3, 4), but

this is the first report, to our knowledge, of a link between seasonal affective disorder and cocaine abuse.

CASE REPORTS

Case 1. Mr. A, a 32-year-old male construction worker, reported that his "winter depressions," which lasted from mid-November to February, started when he was 14 years old. He was born in the Northeast United States and had spent all of his life in the same geographical area. He described annual periods, 3½ months long, that were characterized by hypersomnia, weight change (a gain before cocaine use followed by a 10-20-lb loss when he began using the drug), poor concentration, anergia, anhedonia, marked social withdrawal, and occupational dysfunction. He experienced none of these symptoms nor any manic or hypomanic behaviors at other times during the year. This clinical picture met *DSM-III-R* criteria for major depression, recurrent, seasonal pattern. Mr. A denied any family history of affective disturbance, substance abuse, or other psychiatric disability. He could not identify external precipitants other than the time of year for his periodic depressions.

Mr. A began to use small amounts (less than 1 g/month) of cocaine intranasally at age 19 during a euthymic phase. At

Received May 23, 1988; revision received Sept. 22, 1988; accepted Sept. 30, 1988. From the Department of Psychiatry and the Substance Abuse Treatment and Research Dependence Unit, Yale University School of Medicine, New Haven, Conn., and the West Haven VA Medical Center. Address reprint requests to Dr. Satel, Mental Hygiene Clinic, G7W, West Haven VA Medical Center, West Spring St., West Haven, CT 06516.

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age 20, he increased his cocaine use to 2–4 g/week i.v. during the months of November through February.

Cocaine use during this period helped briefly to ameliorate dysphoria, difficulty concentrating, apathy, and social withdrawal. Mr. A felt that cocaine was helpful, but it did not restore his normal mood. Like some other self-medicating patients (2, 3), Mr. A did not use cocaine in binges to stabilize his mood; instead, he used small doses at several-hour intervals throughout the day.

Mr. A came to our clinic in early spring. His cocaine consumption at that time had reverted to occasional recreational weekend use. Phototherapy was considered for mid-fall, but he was lost to follow-up before this could be initiated.

Case 2. Mr. B, a 29-year-old male middle-level manager, had a pattern of seasonal affective disorder similar to Mr. A's except for the following details. Mr. B first noted symptoms of seasonal affective disorder at age 21. He began to use cocaine at age 24, and he first used it to medicate his seasonal mood dysfunction 3 years before seeking treatment. During the same 3-year period, he did not use cocaine during euthymic periods, describing no craving for the drug during these periods. His cocaine craving paralleled his seasonal mood symptoms directly. Mr. B was not using cocaine when he sought treatment, but he was experiencing craving as his affective symptoms, particularly dysphoria and hypersomnolence, mounted. He sought help in sustaining abstinence as his craving increased. Mr. B declined phototherapy; his symptoms responded to desipramine.

DISCUSSION

The cases of these two patients demonstrate that patterns of cocaine use and craving can parallel the course of an endogenous affective state. Our observations suggest that seasonal patterns of cocaine use

should be evaluated in cocaine abusers to discern whether seasonal affective disorder might also be present. Self-medication of various comorbid axis I disorders may be part of the presentation in up to 50% of treatment-seeking cocaine abusers (3, 4). Cyclical self-medication with cocaine has been reported in individuals with bipolar disorder (2), but this is the first report, to our knowledge, of "seasonal" self-medication with cocaine. The dysphoric symptoms of seasonal affective disorder (1) are comparable to those of cocaine withdrawal (4). Both appear to respond transiently to administration of cocaine, and recent findings for both disorders (4, 5) suggest a possible dysregulation of dopaminergic reward and activation systems.

Finally, the direct link of cocaine craving to an endogenous cue, subjective mood, illustrates the need to supplement current investigations of environmental cues for cocaine abuse with increased attention to sustained but shifting internal mood states.

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Carbamazepine Treatment for Benzodiazepine Withdrawal

Richard K. Ries, M.D., Peter P. Roy-Byrne, M.D., Nicholas G. Ward, M.D.,
Vernon Neppe, M.D., Ph.D., and Sam Cullison, M.D.

Nine patients were given carbamazepine before rapid discontinuation of benzodiazepines. Most patients had had long-term benzodiazepine treatment and had abused benzodiazepines; five had taken high doses. All patients tolerated rapid discontinuation well and none developed significant withdrawal symptoms. (Am J Psychiatry 1989; 146:536-537)

Benzodiazepines have received a great deal of attention in terms of possible toxicity as well as therapeutic effects (1-4). Although new agents and uses have developed (3, 4), so have significant problems of dependence and withdrawal, especially with the newer agents (5, 6).

Recently, Klein and colleagues (7) reported on the use of carbamazepine to facilitate withdrawal from alprazolam in three panic disorder patients who were unable to tolerate a gradual taper. Two anecdotal reports described this use of carbamazepine in Switzerland and Scandinavia (8, 9). In this report we expand on the number of cases for which carbamazepine has been used for benzodiazepine withdrawal. We document its efficacy in patients with psychiatric illnesses other than panic disorder, with benzodiazepines other than alprazolam, and with both high- and low-dose ranges of benzodiazepines.

METHOD

The nine patients studied were hospitalized either on a university hospital inpatient psychiatric ward or in a private substance abuse treatment center. Diagnoses were as follows: psychoactive substance dependence (N=5), panic disorder (N=2), panic disorder and depression (N=1), and bipolar disorder (N=1). They were started on a regimen of carbamazepine on an open basis by one of us before or concurrent with

benzodiazepine discontinuation. Dose of carbamazepine and time for conversion from the benzodiazepine to carbamazepine were determined by the treating physician on the basis of observed withdrawal symptoms. More symptoms prompted higher carbamazepine dose (if tolerated) and slower taper. All patients received at least two 200-mg doses of carbamazepine on the first day if the initial dose was tolerated. Vital signs and benzodiazepine withdrawal symptoms were monitored at least three times a day in both settings. There were standing orders for benzodiazepines as needed (related to the type and dose that the patient had been taking) if active withdrawal developed, as evidenced by 1) diaphoresis or tremulousness or 2) increase in pulse or blood pressure greater than 40% of baseline resting values.

RESULTS

Table 1 presents data on the nine patients successfully treated with carbamazepine for benzodiazepine withdrawal. No patient required benzodiazepine supplementation, and none suffered appreciable withdrawal, as specified earlier. In fact, both patients 1 and 2 had a slight decrease, on average, of their systolic and diastolic blood pressures, as well as of their pulse rates, over the week after benzodiazepine withdrawal (patient 2 had a decrease in blood pressure from 122/80 to 110/72 mm Hg and a decrease in pulse rate from 96 to 84 beats/minute). Accurate sleep graphs were not available; however, sleeping problems were noted only in the progress notes of patient 9 and were rated as mild.

DISCUSSION

These cases provide further evidence of the possible utility of carbamazepine in treating benzodiazepine withdrawal. In this diagnostically heterogeneous population, benzodiazepine discontinuation with carbamazepine was both more rapid and better tolerated than gradual taper alone. Although no systematic ratings were obtained, the absence of benzodiazepine supplementation, noted to be one of the best measures of withdrawal (1), shows that patients did not experience major withdrawal symptoms. Five patients had been

Received July 12, 1988; revision received Oct. 20, 1988; accepted Oct. 27, 1988. From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle; and Harborview Medical Center. Address reprint requests to Dr. Ries, Department of Psychiatry, Harborview Medical Center, 325 9th Ave., ZA-99, Seattle, WA 98104.

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TABLE 1. Clinical Characteristics of Nine Patients Treated With Carbamazepine for Benzodiazepine Withdrawal

Patient	Age (years)	Sex	Drug Regimen		Dose Change (mg/day)	Days for Change	Withdrawal Symptoms	Follow-Up (days)
			Dose (mg/day)	Duration				
1 ^a	34	F	Chlordiazepoxide, 2000	>1 month	Benzodiazepine, 2000 to 50 Carbamazepine, 0 to 800	3 3	None	34
2 ^a	42	F	Alprazolam, 10	2 months	Benzodiazepine, 10 to 0 Carbamazepine, 0 to 600	3 3	Mild anxiety	90
3	28	F	Alprazolam, 3	3 years	Benzodiazepine, 3 to 0 Carbamazepine, 0 to 600	1	None	24
4	66	F	Diazepam, 20	5 years	Benzodiazepine, 20 to 0 Carbamazepine, 0 to 400	1	None	26
5	41	F	Diazepam, 180	1 year	Benzodiazepine, 180 to 0 Carbamazepine, 0 to 600	1	None	22
6	38	F	Clonazepam, 8	6 months	Benzodiazepine, 8 to 0 Carbamazepine, 0 to 600	5	None	3
7	30	F	Alprazolam, 1.5	6 months	Benzodiazepine, 1.5 to 0 Carbamazepine, 0 to 600	4	None	5
8 ^a	31	M	Alprazolam, 15	1 year	Benzodiazepine, 15 to 0 Carbamazepine, 0 to 800	5	None	8
9	35	F	Alprazolam, 10	1 month	Benzodiazepine, 10 to 0 Carbamazepine, 0 to 600	6 3	Muscle twitch	20

^aFailed previous attempt to taper benzodiazepine use.

receiving extremely high doses of benzodiazepines, and three patients had failed previous attempts to taper their doses. Carbamazepine was discontinued 3–14 days after the benzodiazepines without symptomatic worsening. At present, it is unclear for how long carbamazepine should be given after benzodiazepine discontinuation.

Currently, carbamazepine's mechanism of action is unclear. Carbamazepine has no effect on central benzodiazepine receptors or on the larger γ -aminobutyric acid-benzodiazepine receptor-chloride ionophore macromolecular complex (1). Its ability to inhibit electrical excitation in the limbic system may be important (9) in view of evidence that benzodiazepine inverse agonists can produce long-lasting brain changes through a "kindling" effect (10). Other possible mechanisms include its effect on peripheral benzodiazepine receptors and its possible role in indirectly suppressing the activity of corticotropin-releasing hormone (8).

It is important to note that these patients were managed in an open clinical manner by a variety of physicians. Neither patients nor staff were blind to doses, blood pressures, or other variables that would need to be controlled for in a scientifically valid study. Because a number of nonpharmacological variables may positively or negatively affect withdrawal symptoms and tolerance (1), a double-blind study needs to be done

and systematic measures of mood and autonomic arousal obtained to document carbamazepine's efficacy.

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Behavioral Hyporeactivity to Physostigmine in Detoxified Primary Alcoholics

David S. Janowsky, M.D., S. Craig Risch, M.D.,
Michael Irwin, M.D., and Marc A. Schuckit, M.D.

Changes in anergia/inhibition, mood, and pulse rate induced by intravenous physostigmine were significantly less pronounced in 26 patients with primary alcoholism than in 36 normal control subjects. These results suggest possible abnormalities in central cholinergic functioning in primary alcoholics.

(Am J Psychiatry 1989; 146:538-539)

Intravenous infusion of physostigmine, a centrally active cholinomimetic agent, leads to a behavioral syndrome consisting of anergia and fatigue, slowed and decreased thoughts, mild sedation, expressionless face, decreased spontaneous activity, and, occasionally, depression, nausea, or vomiting (1-3). In addition, in individuals with affective disorders, physostigmine has anti-manic properties (1), can worsen preexisting depressive symptoms (4, 5), and may cause transient recurrences of depressive symptoms in euthymic patients (5, 6).

To our knowledge, no investigation to date has specifically reported on the relative behavioral effects of physostigmine in subjects with histories of primary alcoholism. To further understand the diagnostic specificity of the physostigmine syndrome, we explored the cognitive, behavioral, and mood effects of physostigmine in subjects with primary alcoholism.

METHOD

This study was part of a larger study on the effects of physostigmine. The U.S. Food and Drug Administration granted Investigational New Drug status to the study, and the local human subjects committee gave its approval. The subjects were 26 men, aged 18-55 years, who gave written fully informed consent to participate. They each received a psychodiagnostic inter-

view with the Schedule for Affective Disorders and Schizophrenia (SADS) (7), and a Research Diagnostic Criteria (RDC) (8) diagnosis was established by a diagnostician. The diagnosis was based on the SADS interview and collateral information obtained from previous hospitalizations, medical records, and interviews with family members when possible.

All 26 subjects were physically healthy, as determined from their histories and physical and laboratory examinations, were free of psychotropic medications, and had abstained from alcohol for at least 10 days before the study. They all met the RDC for alcoholism before the onset of another major psychiatric disorder (9) and had no other psychiatric illnesses. They were all inpatients recruited from either the Mental Health Clinical Research Center or the Alcohol Research Center of the San Diego Veterans Administration Medical Center. We also studied 36 normal volunteers, who were extensively evaluated with personal and SADS interviews and had normal drinking patterns and histories. The control subjects and patients with primary alcoholism did not differ significantly in age.

As described previously (6), we used a random-assignment, double-blind counterbalanced order design to administer physostigmine and placebo. The subjects were pretreated with methscopolamine (1.0 mg i.m.), and subsequently received intravenous physostigmine salicylate (0.022 mg/kg of body weight) or intravenous saline over a 10-minute period. Methscopolamine and the alternative intravenous infusion were administered 2 or more days later. As described elsewhere, the subjects rated themselves with the Profile of Mood States (POMS) and the Self-Report Activation-Inhibition Scale (1, 5) before and after the infusions. They were rated at the same time by raters using the Brief Psychiatric Rating Scale (BPRS) and the Rater Activation-Inhibition Scale (1, 5).

We analyzed the changes in self and observer ratings from before to after physostigmine (or placebo) administration, covarying for baseline differences between the two groups by using an analysis of variance.

RESULTS

In both the control subjects and the patients with primary alcoholism, the changes in observer and self-

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TABLE 1. Behavioral and Physiologic Responses to Physostigmine in 26 Patients With Primary Alcoholism and 36 Normal Control Subjects

Variable	Change in Mean Value ^a		F ^b	p
	Primary Alcoholism	Control Subjects		
Behavioral ratings				
Brief Psychiatric Rating Scale				
Depression	2.3	3.6	5.5	<0.05
Anergia	1.9	3.2	4.0	<0.05
Excitement	0.2	-0.1	3.7	n.s.
Thinking disorder	0.3	0.3	0.0	n.s.
Psychotic	1.4	2.2	0.6	n.s.
Total	6.6	7.4	2.7	n.s.
Rater Activation-Inhibition Scale				
Inhibition	9.2	18.2	9.2	<0.001
Activation	-2.1	-3.7	2.4	n.s.
Dysphoria	6.8	1.0	0.1	n.s.
Self-Report Activation-Inhibition Scale				
Inhibition	11.8	23.2	4.1	<0.05
Activation	-1.3	-3.1	0.5	n.s.
Dysphoria	1.0	2.0	0.8	n.s.
Profile of Mood States				
Vigor	-5.8	-10.0	12.3	<0.001
Confusion	2.6	6.5	9.2	<0.001
Elation	-2.3	-4.9	6.5	<0.01
Friendliness	-4.0	-7.9	6.3	<0.05
Depression	2.1	6.6	0.3	n.s.
Tension	5.3	7.3	0.5	n.s.
Anger	2.7	2.9	0.1	n.s.
Fatigue	5.6	7.7	2.0	n.s.
Blood pressure (mm Hg)				
Systolic	7.4	12.2	2.5	n.s.
Diastolic	6.4	8.5	1.4	n.s.
Pulse (beats/min)	9.3	19.9	9.4	<0.001

^aMean±SD values before and after physostigmine administration are available on request.

^bdf=1, 61.

ratings of behavior after physostigmine administration were significantly different from the changes after placebo infusion. The subjects with primary alcoholism were significantly less reactive to physostigmine, according to both observer ratings and self-ratings, than the control subjects. As shown in table 1, the alcoholic patients experienced significantly less change in pulse and in the scores on the BPRS anergia and depression subscales, the rater and self inhibition subscales, and the POMS vigor, elation, friendliness, and confusion subscales.

DISCUSSION

Previous studies (6) have suggested that some patients with affective disorder may be behaviorally hyperreactive to intravenously administered physostigmine and other centrally active cholinomimetic agents. However, the results of the present study suggest that

patients with primary alcoholism may actually experience less pronounced behavioral, mood, and physiologic effects of physostigmine than normal subjects.

Although all the subjects with primary alcoholism had abstained from alcohol for at least 10 days before the study, at least some of the behavioral and cognitive effects of alcohol abuse may persist from 6 months to a year after the cessation of drinking. Thus, whether the hyporesponsivity to physostigmine observed in this study in primary alcoholics reflects a true trait cannot be determined without further study.

In any study of the pharmacological effects of a drug on alcoholics, possible differences in peripheral (i.e., hepatic and other) drug metabolism between patients and control subjects must be considered. These peripheral metabolic differences could account for the differences in this study between primary alcoholics and control subjects in the observed behavioral and cognitive effects of intravenously administered physostigmine. However, all of the subjects in the present study were medically healthy. Their liver function test results were within the normal range, as were other laboratory indices. Furthermore, in the subjects with primary alcoholism the behavioral and cognitive effects of physostigmine were not statistically related to liver function. Nevertheless, the possibility that the differences were due to reduction of physostigmine levels by induced liver enzymes cannot be resolved without pharmacokinetic studies. Similarly, the possibility of a difference between groups in smoking habits, leading to a difference in physostigmine metabolism, cannot be absolutely ruled out.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHOANALYSIS

Projection, Identification, Projective Identification, edited by Joseph Sandler. Madison, Conn., International Universities Press, 1987, 216 pp., \$27.50.

American psychoanalysis, once the protected domain of ego psychology, has experienced a continuing and no longer subtle thrust toward varieties of object relations theories, many of which are rooted in the original work of Melanie Klein. This change, in part reflecting a worldwide Kleinian influence, has been one important element in the growing diversity of theories that characterizes American psychodynamic thinking today and reflects the growing vigor of British psychoanalysis in the United States. The versions of Kleinian thought that have taken root here are removed, for the most part, from what might be called the radical Kleinianism of both her original followers and some of the current European Kleinian schools. The volume under review here has taken a key clinical concept of Klein's—projective identification—and subjected it to thorough scrutiny by a diverse group of eminent analytic theorists and practitioners. They not only illuminate the concept in question but also show how analysts of disparate schools view clinical data and talk to their patients.

The book originated in a conference held in Jerusalem in 1986 under the auspices of the Sigmund Freud Center of the Hebrew University of Jerusalem and organized by Joseph Sandler, then the Sigmund Freud Professor of Psychoanalysis. Four papers were presented then, and two additional papers have been added to round out this volume. An introductory chapter by Sandler and Perlow is followed by papers by Sandler, W.W. Meissner, Betty Joseph, Otto F. Kernberg, Rafael Moses, and Yoram Bilu. Most of the papers are rich in detailed clinical material, making it possible for readers to make their own judgments concerning fit of interpretation to patient. Each paper is followed by a discussion among conference participants led by Dr. Sandler, who does a splendid job of focusing the discussion, challenging obfuscations, and clarifying concepts. The book is also an extension of Sandler's continuing exploration of the processes of internalization and representation. Only one of the contributors, Meissner, contests the very existence of the phenomenon of projective identification; the others all begin with a belief in its clinical value, differing only as to how it is to be conceptualized and applied. The general problems of research in psychodynamic concepts are evident in the fact that although almost all of the participants hold projective identification to be an essential element in their clinical work, each thinks about the phenomenon quite differently. Each of the chapters has merit, and the level of the contributions is unusually high for a collection of papers, but I will discuss only a few of the papers here.

Sandler, in "The Concept of Projective Identification," outlines with admirable clarity and simplicity the growth and elaboration of the concept from the original, fairly straight-

forward description by Klein. Sandler describes it as a central and necessary Kleinian clinical concept, now increasingly used by analysts of other theoretical leanings. In Klein's original description, projective identification was a consequence of the infant's defensive and adaptive direction of self-hatred toward the mother. Klein said, "This leads to a particular form of identification which established the prototype of an aggressive object relation. I suggest for these processes the term 'projective identification'" (p. 15). Sandler emphasizes that these processes can be considered as occurring in fantasy and involve mechanisms of splitting of parts of self and object, projection, and identification. Sandler describes Klein's definition as the first stage in the development of the concept of projective identification. In the second stage, he says, Heimann, Racker, and others extended the concept by connecting it with the analyst's countertransference through the analyst's identification with the projected object or with the feelings projected onto (or into, the Kleinians say) him or her by the patient, with which the patient maintains continuing identification. These countertransferences, in which analysts feel that they have the qualities of the object that the patient has projected, become an important source of information concerning the patient's inner representations. In what Sandler refers to as the third stage of projective identification, mainly a result of the ideas of Bion, the patient succeeds in putting parts of the self or internal object into the analyst, who now serves as a "container." In this view, the transfer of psychic contents from patient to analyst is not only a fantasy but is regarded as a concrete process. Sandler goes on to give a lucid discussion of the many issues raised, expanding on matters of control, the self-object boundary, the "holding function" of the analyst, and other basic ideas. He ends his chapter with a caution against using projective identification, a descriptive concept, as a pseudoexplanation, warning that analysts cannot comfortably assume that all their countertransference responses have been put "into" them by the patient: "Unfortunately, the differentiation of what belongs to the patient and what to the analyst is likely to remain with us for some time as a difficult clinical problem" (p. 26). Not all of the authors in the book heed this warning.

Meissner's chapter is likely to strike many U.S. analysts as most sensible. He would confine projective identification to Klein's original usage, and he is at special pains to avoid any theorizing that reifies ideas or treats fantasies and representations as concrete objects and processes. Such reification is exemplified by the statement of one of the discussants: "Anyone who has worked with schizophrenics in a mental hospital will have seen how they split off and push bits of themselves into a variety of different people in the institution. Then, of course, they have to spend their lives going around from one to another, attending to these different bits of themselves" (p. 62). Not everyone would see the mental lives of schizophrenic patients so graphically, although we probably can agree that patients have such fantasies.

Betty Joseph, in a very crisp discussion, emphasizes the communicative aspect of projective identification and its cen-

trality for understanding countertransference responses and, hence, the patient. She also stresses that there are multiple forms of projective identification. However, skeptical readers may feel that in each of her cases one can explain the material as easily by assuming the analyst's skill in understanding and empathizing with the communications of the patient, including projections and identifications, without invoking the concept of projective identification. That patients can and do induce noxious feelings in us that they themselves have experienced and hate does not necessarily require that we conceive of the feelings being emptied from them into us. In several of Joseph's cases there is clear evidence of projection of unwanted feelings, but the patients seem much more intent on denying and disavowing their feelings and the evidence for their identification with them in the analyst seems slim. The analyst's recognition and experience of the states projected do not require that the patient has, in fact, assumed magical control of the analyst because the analyst now contains a part of the patient. This may be more a matter of style of conceptualizing, because Joseph gives graphic proof of great sensitivity and close emotional attunement to her patients. I believe most analysts would have little difficulty understanding her conversations with her patients; some would, however, describe the interventions in different language. Joseph makes clear that she views projective identification as a mechanism and puzzles about how it works ("How do they get stuff into us?" [p. 91]), but without recourse to what little we know about modes of communication between mothers and children. She is also clear that "defenses start at the beginning of life" (p. 92) to protect the child against overwhelming anxiety, and it is here, perhaps, that Kleinian analysts are farthest away from other analytic thinkers.

Kernberg is exceptionally lucid in describing his view of projective identification. He defines it as "a primitive defense mechanism" consisting of "projecting intolerable aspects of intrapsychic experience onto an object," "maintaining empathy with what is projected," "attempting to control the object as a continuation of the defensive efforts against the intolerable intrapsychic experience," and "unconsciously inducing in the object what is projected in the actual interaction with the object" (p. 94). He regards it as a primitive defense used under conditions of unbearable affective experience, compared with introjection and projection, which are higher-level defensive processes. He presents three vivid case vignettes to demonstrate how projective identification appears and is interpreted with patients of differing levels of psychopathology. He is clear that patients induce these countertransferences by their behavior toward us, implicitly rejecting the idea that feelings and objects are placed in another person.

The final two papers of the volume, Moses's chapter on the relation of projective identification to political process and Bilu's on the myth of *dibbuk* possession, are original and a pleasure to read.

Although the book focuses our attention on the title concepts, it is a superb opportunity to read about how skilled analysts are dealing with complex clinical issues and how analysts of differing schools can inform each other and exchange ideas productively. Despite the definitional confusion that exists around so many vital psychoanalytic concepts, the shared clinical and theoretical base is now so substantial that these differences become sources of new information rather than failures of communication. The book, thanks in large part to Sandler's humor and incisive comments, reads

smoothly. I recommend it highly. It is a superb example of psychoanalysis at its current best.

ARNOLD M. COOPER, M.D.
New York, N.Y.

The Freud/Jung Letters: The Correspondence Between Sigmund Freud and C.G. Jung (1974), edited by William McGuire; translated by Ralph Manheim and R.F.C. Hull. Cambridge, Harvard University Press, 1988, 650 pp., \$15.95 (paper).

The correspondence between Freud and Jung is to me the single most important piece of documentation about the history of psychoanalysis to have appeared in the last 20 years. When these letters first appeared in 1974 (1), they sent shock waves through the intellectual community. It was the first time that Freud had been allowed to appear in an untendentially edited way. Although the Jung family insisted on making cuts in Jung's words, the Freud family had at last wisely decided to let Freud speak for himself.

Even some sophisticated observers were startled at how outspokenly unlike his stereotype Freud could be. The vested interests of organizational life keep wanting to use Freud to defend the status quo, but the real Freud is far more interesting than his true believers would make him appear. Freud was subversive of received wisdom and conventional understanding.

Ernest Jones, Freud's official biographer, thought this set of letters was the best of all the Freud correspondences. From the point of view of intellectual historians, they are an indispensable part of our century's life of the mind. Freud and Jung started out from different backgrounds and perspectives, and it is a tribute to them both that their intimacy lasted as long as it did. Jung's wife, Emma, sent Freud some particularly poignant letters as she tried to stave off the breach that grew up between the two men.

It is one of the ironies of our time that Freud, a neurologist with almost no psychiatric training, was to have so much more of an impact on North American psychiatry than Jung himself, even though Jung came from the best traditions of Swiss psychiatry. The European distinction between neurology and psychiatry, which was so important in Freud's own day, is apt to elude American general readers today.

Freud's success with his creation of psychoanalysis is in part a tribute to his superior command of language as well as to the devotion of his followers, who did so much to put his discipline in good shape for historical scholarship. By editing his works carefully the disciples of Freud made sure that his ideas got the best possible hearing. Jung, on the other hand, who from our own perspective looks so prescient about some of the central inadequacies in Freud's way of thinking, has not received anything like his due. Jung did not write as clearly as he might have, and the general biographical understanding of him, his psychology, and his movement is still in its early stages.

Reading these letters is profoundly challenging because both Freud and Jung anticipated most of the problems in twentieth-century psychotherapy. *The Freud/Jung Letters* were magnificently edited by William McGuire, who fulfills the task of keeping the reader expertly informed without engaging in any partisanship. This 1988 edition even has a new preface by McGuire, which I found informative in that it contains material on Sabina Spielrein that has appeared since the publication of Aldo Carotenuto's book (2).

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PAUL ROAZEN, PH.D.
Toronto, Ont., Canada

The Psychoanalyst in Psychiatry, by Thomas Freeman. New Haven, Conn., Yale University Press, 1988, 193 pp., \$25.00.

This is a multifaceted volume that can be approached from various levels. In the foreword, Albert Solnit beautifully captures the essence of the author's ideas and tempts the reader to explore further.

Dr. Freeman is one of the pioneers attempting to apply psychoanalytic treatment principles to the treatment of severely emotionally disturbed patients, particularly those with schizophrenia. His works have not been widely noticed in the United States, which is regrettable because there is much to learn from the wisdom he has accumulated from his rich clinical experience.

The title of this book is especially apt. Freeman brings a psychoanalytic perspective to psychiatry and assumes that these two areas simply represent mutually enriching viewpoints that augment our understanding of difficult clinical phenomena. He uses a phenomenological orientation that enhances psychoanalytic concepts, especially developmental and structural elements. This is in contrast to those clinicians who have attempted to polarize psychiatry and psychoanalysis.

Freeman refers to positive and negative symptoms as formulated by Bleuler. Positive symptoms include hallucinations, delusions, psychotic rituals, and other forms of behavior, perceiving, and thinking that represent primitive adaptations to the external world. According to Freeman, these emerge when emotional illness becomes manifest. Negative symptoms are expressions of structural and developmental defects, such as defective ego boundaries, poorly structured mental representations (especially the self-representation), and other factors related to the distinction between the inner and outer world and reality testing. Freeman emphasizes, as have several recent articles in psychiatric journals, that neuroleptic drugs can cause positive symptoms to disappear but they do not have any substantial effect on negative symptoms. He concludes that psychopharmacological agents have no effect on basic structure and that the best the patient can hope for from drug regimens is the achievement of the status quo ante. In many instances, however, this is a desirable goal.

Freeman extends some of Hughlings Jackson's hierarchic concepts of structure as well as the more clinical orientations of Wernicke and Bleuler to the study of psychopathology and the treatment process. These concepts are germane to the predictability of the course of illness. He concentrates on integrative-projective processes, but he prefers to use Bleuler's language, referring to these mechanisms as "appersonation" and "transitivity."

Schizophrenia is viewed from both a longitudinal and cross-sectional approach. From certain phenomenological observations regarding the history and course of the illness, the author reaches conclusions about psychic structure (cross-sectional perspective) and the primitive interactions

with reality as they are reflected in the content of delusions. Again he emphasizes what effects drugs can have on various structural configurations as well as the role of psychoanalytic treatment.

I recall a patient whose psychic structure was reflected in his dreams and how they changed after he received haloperidol. Before medication he would dream of being in forests filled with dangerous devouring animals and in disease-infested swamps full of rotting vegetation and dead bodies. His paranoid orientation was reflected in his better-structured dreams in which he was surrounded by persecutors, as occurred in the forest dreams. After several weeks of taking haloperidol, he had a dream in which he was at a carnival where everything was fun and thrilling. He described the exhilaration produced by the rides. Below the ground, however, in subterranean lakes, were dead rotting bodies. Apparently the surface aspects of his psyche as they related to the external world had changed, most likely the effect of medication, but the deeper layers of his psyche remained the same. Many psychotic patients demonstrate a discontinuity of character in which there is no smooth hierarchic blending of psychic structure from lower to higher levels and from primary process to secondary process operations.

This book is interspersed with clinical vignettes to translate concepts about nosography, psychotic identifications, the content of delusions, psychic development and childhood illness, and other clinically relevant topics into palpable illustrations. Some of these seem to be cliffhangers, however, because the author's psychodynamic forays do not go far enough nor is he specific about the treatment interaction. It is as if the psychoanalytic frame has been somewhat diluted by the psychiatric perspective. This is all the more frustrating because Dr. Freeman convincingly demonstrates that the clinician can achieve a greater depth of understanding by the combination of these two approaches.

Perhaps in the future Dr. Freeman can furnish us with more in-depth formulations about the psychotic process, a welcome addition to the valuable insights he has provided in this volume.

PETER L. GIOVACCHINI, M.D.
Chicago, Ill.

DREAMS AND DREAMING

The Theatre of the Dream: New Library of Psychoanalysis, 6, by Salomon Resnik; translated by Alan Sheridan; David Tuckett, general editor. London, Tavistock, and New York, Methuen, 1987, 207 pp., \$45.00.

French psychoanalytic writing has always been in much closer touch with the mainstream of thinking in philosophy, literature, and linguistics than has the psychoanalytic literature in English-speaking countries. Jacques Lacan and Paul Ricoeur, for example, have assumed in their readers a familiarity with the major intellectual currents of the day that never could have been assumed or drawn upon by writers in English-speaking countries. Salomon Resnik's short exploration of dreaming is very much in this tradition and assumes at least a passing acquaintance with the philosophies of Husserl and Heidegger, the linguistics of de Saussure, and the psychology of Jung, to say nothing of major European literary figures and the major schools of psychoanalytic thought.

Resnik's clinical work draws heavily from the English Kleinians, especially Wilfred Bion.

The book, much like psychoanalysis itself, is an associative adventure. Resnik's purpose is to expand the conceptualization of the entire "theatre" of the dream world—not just as a flat verbal text, handed to the analyst and assumed to have a single meaning, but as a true somatic and symbolic intersubjective event involving the analyst and the analytic process. Resnik explores the relationship of the dream to body, to symbol, to language, to myth, to psychosis, to poetry, and, above all, to the dreamer's audience, the "other," the intersubjective blend of transferences and countertransferences within which psychoanalytic work takes place. Resnik's explorations form an ever-expanding commentary on the dream as a bodily, symbolic, and creative event and on the nature of the psychoanalytic process itself. The text, too discursive and branching to adequately describe or summarize, is filled with marvelous clinical vignettes and brilliant philosophical insights brought to the clinical situation. The book offers the psychoanalytic initiate a marvelous opportunity to expand the notion of what a dream is and how the dream reality comes to bear on the immediacy of the clinical situation.

This is a difficult book to evaluate. There is much in the way of clinical brilliance and philosophical profundity, but the reader wanting to tease out what the actual premises are that support Resnik's thought may find that task perplexing. At times, his clinical vignettes require the reader's faith that his interventions were based on associative material. His clinical approach generally and his enigmatic method of discourse specifically will have a familiar ring to those who knew the late Wilfred Bion, to whom the book is dedicated. This is a demanding and sometimes disturbing book that offers a great deal to those who have the background in psychoanalysis and modern European intellectual thought and can withstand the ambiguity that Resnik's ideas and style demand. For those with that background, who can both tolerate and appreciate the uncertainty and see it as appropriate to the quest for an understanding of the patient's imagination, waking and sleeping, the book is highly recommended.

MELVIN R. LANSKY, M.D.
Los Angeles, Calif.

The Dreaming Brain, by J. Allan Hobson. New York, Basic Books, 1988, 336 pp., \$22.95.

This book is both a delight and a disappointment, depending on whether you read it to learn about the brain or about dreams. The book attempts to look at dreaming both from a bottom-up neurobiological and a top-down phenomenological perspective. Mostly the bottom-up prevails and is the strong aspect of the work. What Dr. Hobson does here is superb. He lays out the history of the interest in dreams as universal, intriguing phenomena that defied much progress in their understanding until early in this century. At that time, with the development of the EEG for recording electrical activity and changes and the development of methods for studying the neurochemistry of the brain, the scene was set to study the differences between the various states of consciousness—waking, sleeping, and dreaming. This is what Dr. Hobson knows well, as he has been a major contributor to mapping the mechanisms by which dreaming sleep, REM, is turned on and off.

We learn not only the history of these discoveries and how the knowledge of the brain's activities around the clock was built on by each major investigator in turn, but also how this knowledge was tested by experimental manipulations that now can control the decrease and increase of REM sleep through microinjections of cholinergic agonists and antagonists at different sites.

This is the bottom-up story, which occupies the first two-thirds of the book. Dr. Hobson then turns to dreams, the Hobson-McCarley activation synthesis theory of how dreams are formed, and its contrast to the psychoanalytic theory. Basically, the Hobson-McCarley theory sees dream construction as a "meaning-added process." That is, dreams are built up from "signals of low informational order to a higher order final product (the dream as narrative)," and the brain does its best to achieve a "meaningful integration of data, even if it must resort to creative story telling."

Once this theory is stated, the book turns to test it on the dreams reported in a diary and illustrated by line drawings of a man who recorded 233 dreams for a few months in 1939, a strange sample to choose for a laboratory scientist. The man could not be interviewed to tap his characteristic "persistent concerns," nor could his sleep before the dream report be analyzed for the directionality or density of his eye movements. If the brain adds meaning from the individual's persistent concerns to synthesize and account for the activated state from the brainstem stimulation expressed at the surface as rapid phasic movements of the eyes, why abandon the very tools for bridging from neurophysiology to psychology that have worked so well in getting us this far?

In his defense, Hobson offers some dimensions of content and form from his study of the diary of dreams: persons, places, bizarreness, and movement that are useful in analyzing and comparing dreams and dreamers in future work. The book is well written and beautifully illustrated, but it needs a companion top-down volume.

ROSALIND D. CARTWRIGHT, PH.D.
Chicago, Ill.

Freud's Self-Analysis, by Didier Anzieu. Madison, Conn., International Universities Press, 1986, 618 pp., \$60.00.

At first glance, the burgeoning interest in French psychoanalysis in the United States seems perplexing. Psychoanalysis took root most strongly here; from the 1930s onward, psychoanalysts in the United States seemed confident that their expansion of psychoanalysis was the ultimate expression of psychoanalytic development. True, attention had to be paid to Anna Freud and her followers, but their work seemed to closely parallel much that was important in the United States. Suddenly, however, in the last 5 years names such as Chasseguet-Smirgel, Derrida, Lacan, and MacDougal all figure prominently in the American psychoanalytic literature. Although these psychoanalysts can hardly be said to present a uniform set of contributors and in fact do not at all agree with each other, they share a style of presentation that is distinctly French. By this I mean they are more dramatic in their dedication to the primary importance of the content of the unconscious and less interested in a developmental model of personality. The fact that French psychoanalysts see themselves as returning to Freud and frankly embrace a hermeneutic approach distinguishes them from their more scientifically oriented colleagues in the United States.

Psychoanalytic theory in the United States has tended to be dominated by the structural hypothesis and by ego psychology, as represented in the work of Brenner and Arlow as well as other so-called classical psychoanalysts. This approach, with its emphasis on understanding all psychological phenomena in terms of compromise formation involving the product of a clash between drive and defense, has seemed to many psychoanalysts, myself included, to limit the flexibility necessary in conducting a therapy as complex and two person in nature as psychoanalysis. This, in turn, produced an interest in alternative approaches in theory, such as those represented in the writings of French psychoanalysts. The tendency of classical psychoanalysis to remove the psychoanalyst from participation in unavoidably and not regretably influencing the nature of the transference has led to growing dissatisfaction with what I would call establishment psychoanalytic theory. This dissatisfaction in turn has resulted in a restless search for the expansion of theory that would infuse psychoanalysis with a newfound vigor and sense of challenge. Ironically, French psychoanalysis, with its emphasis on a return to Freud, results in a theory less bound by the limits of instinct and defense because the return to the original Freudian text becomes a vehicle that permits a deconstructionist dismantling of Freud. The resultant construction of theory, whether by Lacan or Chasseguet-Smirgel, leads us not into a more orthodox interpretation of Freud but into an extension of theory that reflects the mind, experience, and opinion of the current author. This is the Freudian text used as the launching platform for the interpretative energies of the new contributor.

This volume represents the translation of a two-volume book first published in French in 1975. It cannot be said to be a biography in the usual sense of the term but it nonetheless covers much biographical material. It is a unique attempt to use Freud's written record of his dreams as well as his letters to Fleiss to reconstruct a brief period in Freud's life when, in Anzieu's view, he invented psychoanalysis through his self-analysis. The delay in translation is unfortunate in view of the more recent publication of Peter Gay's definitive biography of Freud (1) and Masson's translation of the complete Freud-Fleiss letters (2), both of which include in a more accessible form much of the material covered by Anzieu. Nonetheless, Anzieu's scholarship and knowledge are immediately apparent. This is undoubtedly the work of a brilliant Freud scholar who knows his way around the events of Freud's life and times. He is familiar enough with Freud to make his speculations regarding Freud's unconscious seem plausible, even convincing. His concern with the details of Freud's life, dreams, and thinking will certainly seem obsessional to most readers and even become discouraging as the author's seemingly endless appetite for such detail outstrips any editorial restraint.

Anzieu's central hypothesis is that Freud conducted a self-analysis, largely through interpretation of his own dreams, during the period between 1895 and 1902 and that through this he in essence discovered all of psychoanalysis. This claim seems exaggerated in view of the productivity of the remaining years of Freud's life. Anzieu finds more in the material he examines than it appears to me to contain. He uses his interpretative skills to assert that what he sees in the material was available to Freud. The conclusions of Freud's self-analysis seem far less grandiose than those claimed for it by Anzieu. Furthermore, placing such emphasis on how much

of psychoanalytic theory is derived from Freud's examination of his own dreams serves to deny Freud's dedication to the clinical approach to patients. Psychoanalysis as the product of one man's introspection is certainly not a view that fits with Freud's efforts to understand the source and meaning of a patient's symptoms and suffering while constructing an overriding theory of psychoanalysis.

This return to Freud emphasizes completeness as well as detail. The author notes that a previous volume by Alexander Grinstein (3), although applying considerable erudition to a study of 18 of Freud's dreams, "was woefully incomplete" compared with his own, which includes 50 dreams, two daydreams, 48 childhood memories, screen memories, parapraxes, and acts of forgetfulness. Furthermore, in his opinion, "Grinstein lays far too much emphasis on the importance of the day's residues for an understanding of Freud's dreams, at the expense of unconscious wishes, defensive conflicts and various mechanisms other than that of symbolic representation." The reader should be aware that the reinterpretations or expanded interpretations of Freud's dreams presented here were arrived at by a group method of "literal interpretation" in which a dream would be read out loud, line by line, for scrutiny. Anzieu feels that through the use of associations by the group members to the dream, a level of meaning beyond the usual level of Freudian concepts could be achieved.

Curiously, these attempts to reinterpret Freud's own interpretations of his dreams seem labored and overburdened by Anzieu's use of detailed knowledge about Freud's life, particularly the nature of his relationships. Twenty-five pages are devoted to adding meanings to Freud's interpretation of the dream of Irma's injection. In Freud's original system of dream analysis, he restricted the use of intuition in interpretations for the obvious reason that he was attempting to invent a scientific method for interpreting dreams. Even in Freud's hands dream interpretation was too closely tied to the associations to each element in the dream. Anzieu not only holds to this particle-like fractionation of the dream but loads each element of the dream down with a plethora of facts that he associates to the dream. Freud's relatively simple interpretations, although possibly missing some aspect of penetrating insight, nonetheless represented his own associations and not those of a team of investigators who were able retrospectively to integrate historical material with the elements of the dream.

In his efforts to invent a science of dream interpretation as well as to perform a self-analysis, Freud was at a distinct disadvantage because he had a limited range of data to work with and a lack of self-awareness, to be expected in an individual who had no psychoanalyst to add outsider insight to his introspection. Freud felt bound to his theory that all dreams must conceal a wish fulfillment. In the Irma dream he could work it around to the wish fulfillment perspective by emphasizing his wish to displace blame for a treatment failure onto an innocent colleague. Although Anzieu finds a multitude of auxiliary interpretations in the material about the exact nature of who was in Freud's life at the time of the dream, he fails to raise any questions about a different kind of meaning in the dream. Could the dream contain a warning about Freud's poor judgment in choosing colleagues? Is this a harbinger of his need to see Fleiss more realistically before he is able to free himself as an independent thinker? Of course, these are questions that defy an exact answer. Per-

haps they are questions that would not even be asked by those who are willing to see Freud's contributions as limited by the historical context in which they were made rather than as texts that require further interpretation to come alive or, rather, to be kept alive artificially.

Anzieu's treatment of Freud's relationship with Fleiss once again highlights the peculiar mixture of elements in Freud's personality. His courting and flattery of Fleiss and his need of Fleiss reflect his use of Fleiss as a self-object. But they also represent the triumph of Freud's need to gloss over the reality of Fleiss's limitations. Retrospectively, we can see the strange nature of Fleiss's theory. Freud could not do so. In the end Freud resorted to depression to liberate himself from his enmeshment with Fleiss. Although Anzieu illustrates this process very well, he denies the fact that the Freud of 1902 was still a far cry from the original thinker whose clinical work would force him to modify over and over again his theories of psychopathology and his method of psychoanalysis.

I am not at all certain that the author's expenditure of effort is warranted by the result he gets. No amount of rationalization will convince more scientifically oriented analysts of the dominance of the id and the unconscious as exclusive determinants of psychological functioning. Freud himself abandoned this early view, perhaps recognizing its link to his fallen self-object, Fleiss.

The reader who undertakes this book should be prepared to be dazzled by the author's erudition. It is an impressive interpretive tour de force. However, the text ultimately sheds light not on Freudian theory or on Freud himself but on the style of psychoanalysis that the author himself prefers. This style, although fascinating, will be confusing to psychotherapists trained in the United States, who have tended to follow Freud in his subsequent movement away from an id-unconscious topographical model. Those who prefer the freedom to speculate as to symbolic meanings and explanations of behavior in terms of deeper meanings will find a good deal to please them in this text. I doubt, however, that even the most enthusiastic followers of the so-called deeper regions of the mind will find the detailed analysis of dream after dream an exercise that can sustain their interest, even though the dreamer is Freud himself.

Those dynamically oriented psychiatrists who wish to find out more about the French approach to psychoanalysis and particularly the emphasis on early Freudian texts as the springboard for theory building would do well to read selected portions of this book. At one level it can be considered "The Interpretation of Dreams Revisited." One dream at a time, however, is all that I can advise. To read more at one time is sure to be an overdose. Such an overdose would in no way be fatal but it could certainly dampen a person's enthusiasm for psychoanalytic theory—not to mention dream interpretation and the contributions of French psychoanalysis.

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HENRY J. FRIEDMAN, M.D.
Cambridge, Mass.

BIOGRAPHY

Erich Lindemann: A Biographical Sketch, by Elizabeth Brainerd Lindemann. Wellesley, Mass., Elizabeth B. Lindemann, 1987, 90 pp., no price listed (paper).

Published nearly a half century ago in the *American Journal of Psychiatry*, Erich Lindemann's "Symptomatology and Management of Acute Grief" (1) is still a frequently cited paper. Reporting his psychophysiological observations on the response of family members to the death of their loved ones in Boston's tragic and disastrous Coconut Grove fire, Lindemann's article focused clinicians' attention on the importance of loss and grief as significant events in human life. His findings made important contributions to a host of subsequent clinical studies, including his own on ulcerative colitis, by elucidating the role of stress in human physical and emotional disorders.

Lindemann's groundbreaking investigations during the 1940s constituted only one of three major stages in his academic and scientific career. These have been admirably and sensitively depicted in this small volume, which, though modestly subtitled "a biographical sketch," manages to paint an intimate and detailed portrait of the man and his work. Written by his wife, a skilled clinical social worker in her own right, the narrative brings Lindemann from his native Germany to the Iowa Psychopathic Hospital in late 1927, where he continued the study of psychotropic drugs that he had begun across the Atlantic at Heidelberg. Even at that early point in his scientific development he evinced a keen interest in the psychological correlates of his subjects' physiological responses to a variety of psychotropic substances and saw the study of their human relationships as a vital dimension of their psychological functioning.

Lindemann's move in 1935 to the Massachusetts General Hospital in Boston initiated the next phase in his intellectual development by exposing him to Dr. Stanley Cobb, whose pioneering work in psychosomatic medicine was a central factor in the evolution of that field. Lindemann's special concern with the individual's human environment, which was evident in his Iowa drug studies, accompanied him to Boston, where it infused his investigation of patients with ulcerative colitis, whose symptoms, he noted, were often intimately related to ruptures in their interpersonal relationships. It was within this context that he seized on the calamitous mischance of the Coconut Grove fire to make extensive studies of the psychophysiology of acute grief.

Although Lindemann became a psychoanalyst and a superb clinician during these phases of his career, it is not surprising that his focus on the interpersonal led him beyond the contemporary preoccupation with intrapsychic dynamic processes to an interest in the individual's social milieu—an interest that finally formed the central motif of the third phase of his professional odyssey as he moved to a study of social networks in the community and their potential for preventing the often catastrophic reactions to the disruptions of individual human relationships. With the formalization of this work when the Wellesley Human Relations Service was created in 1948, Lindemann embarked upon a career in community psychiatry long before that approach became the nationwide blueprint for managing mental illness in the 1960s. That third and final phase of his professional vocation dominated his attention throughout the rest of his life, and he

may with some justification be said to be the founding father of the community psychiatry movement in the United States.

In her felicitously crafted tapestry of her husband's career, the author has not neglected to interweave the warp of his scientific activities with the woof of his own social milieu. She gives an intimate picture of the many human relationships that complemented the unfolding of Lindemann's intellectual accomplishments. He comes alive for us as a son and youthful student in Germany, as a brilliant teacher and head of a major department of psychiatry at Harvard, as an inspiring leader of groups of multidisciplinary scholars, as a musician and father, and above all as a partner in a marriage that was marked by a sharing of public and private endeavors. Elizabeth Lindemann's "biographical sketch" is a historically important and fitting tribute not only to her husband's major contributions to American psychiatry but to their companionship during his life and beyond.

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J.C.N.

PSYCHODYNAMIC AND COGNITIVE THERAPY

Mutative Metaphors in Psychotherapy: The Aeolian Mode, by Murray Cox and Alice Theilgaard. New York, Tavistock Publications (Routledge, distributor), 1987, 276 pp., \$49.50; \$18.95 (paper).

There are therapists who passionately believe that the right language or idiom, the correct "voice," can open the patient's path. This mode of therapy is not dependent so much on a formulation or general theory of human behavior as it is on the tuned heart and ear of the therapist. Murray Cox has previously displayed such perceptions (and the ability of clear communication to the reader) in an earlier book (1). Now he and Dr. Alice Theilgaard encourage therapists to encounter the "Aeolian mode."

Murray Cox is an English senior psychiatrist-psychotherapist. He consults at Broadmoor Hospital, where he has treated some of the extreme criminal offenders in England. He has a scholar's acquisition of the classics and a particular appreciation of Shakespeare.

Dr. Alice Theilgaard is Chief Psychologist at the Copenhagen University Psychiatric Clinic. She is a well-known neuropsychologist with established research in demographic studies on a number of subjects, including (somewhat distant from the present subject) the genetics of sexuality, and is also known as a clinical psychologist and pursuer of mutative interpretations for change in psychotherapy. Dr. Theilgaard is also a Shakespeare scholar.

The Aeolian mode takes its name from the Aeolian harp, which made music with the wind. This mode in psychotherapy depends on the capacity of the therapist to resonate with the nuance of "the patient's story." Using this mode, therapists become increasingly attentive to the patient's presence and use their own associative activity. This form of attention and empathy employs imagery and metaphor. The metaphor can be "mutative" in that it facilitates intrapsychic change and reduces psychic instability. The authors

present this mode as anchored in developmental psychology, neuropsychology, and existential psychology. The mode is nonreductionistic.

The Aeolian mode is described as a complex process composed of at least three dynamic, intertwined, and conceptually separate components. The poetic component is the presentation of a "newly minted" image through metaphor. The therapist also uses his own "fine tuning" to achieve coherence between evoked associative echoes and the patient's inner world.

The therapist finds the tipping point at the moment of "dynamic instability," when the patient is optimally receptive to the therapist's urgent indication for change or "stabilizing reinforcement." The book is rich in poets' words as salient comments on the human condition. The therapist can use poetic ability or borrow (or plagiarize) as appropriate to the patient. A line or phrase comes into the therapist's head, he or she holds it and does not reject it or blurt it out but waits until it shapes into something "usable." Associative reverberations allow the therapist to "wait and to witness" until the moment comes when a mutative metaphor can "touch the depths before it stirs the surface."

The authors present the narrative of patients in a way that conveys respect, empathy, and wonder at the communicative value of human speech. For example, a telephone operator with a severely disabling paranoid disorder describes the calls she receives from the "outside": "When I got anxious, I pulled the wires out. I cut off the boss! I felt cut off and everyone was trying to get through to me." Her history of auditory hallucinations and partial introjects allowed the therapist to construct a metaphoric algorithm in describing her: "I always cut off outside calls." "I never cut off inside calls." Supportive therapy consisted of monitoring and reference to her "switchboard."

This review presents only some of the flavor of the wealth of clinical vignettes, as in this exchange: A furtive, frightened, suspicious—almost paranoid—girl says, "I can't talk to them . . . they know all about me." The therapist answers, "But if they knew *all* about you." The patient finishes the sentence: "If they knew *all* about me, then they'd understand."

This book is for therapists who wish to move toward their own style in psychotherapy and who seek the unique issues in their relationships with patients. This book is not, however, meant to appeal to the untethered therapist making wild interpretations or exercising little control. The authors impose confines and discipline as they speak to extending the therapist's ability (in much the same way that a good athletic coach enjoins his pupil to "extend"). The extension of our own innate poetic, metaphoric reach is now not only the province of the poet. In this book Drs. Cox and Theilgaard stake out this country for the therapist's movement as well.

The authors attempt to meet the challenge of a three-line statement regarding the essence of the Aeolian mode: "Attend. Witness. Wait."

Discern, formulate, potentiate, and reflect mutative material. Attend. Witness. Wait.

Understanding within this "nutshell," however, follows on the process of getting into the text, and that is easy. It is a wonderfully good read. It will carry engaged and attending readers into extensions of their own styles in psychotherapy, whatever their theoretical base. Readers may often have the thought: "I wish I could say something like that." The authors (like good coaches) say to us, "You will, you will."

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THEODORE NADELSON, M.D.
Boston, Mass.

Short-Term Dynamic Psychotherapy: Evaluation and Technique, 2nd ed., by Peter E. Sifneos, M.D. New York, Plenum, 1987, 316 pp., \$34.50.

Well-known among the psychodynamic approaches to brief therapy is short-term anxiety-provoking psychotherapy developed by Peter Sifneos, M.D., Professor of Psychiatry at Harvard Medical School. This second edition of his text on the subject (the original, also published by Plenum, appeared in 1979) expands and updates the systematic exposition of his relatively brief approach (1–20 sessions), involving once-a-week face-to-face treatment interviews, for resolving classical oedipal disturbances. In this edition Dr. Sifneos states,

The nature of the psychological conflicts which are chosen to be resolved, and which underlie the patient's difficulties, are oedipal or triangular. This implies that problems must have developed between the patient and his parents during early childhood and are being repeated in his current interpersonal relations. These problems have to do with a competition with the parent of the same sex for the love and affection of the parent, or a parent surrogate, of the opposite sex. Repetitive unsuccessful attempts to deal with these conflicts give rise to circumscribed symptoms and/or to well-delineated interpersonal difficulties, which act as a compelling force in making the patient seek help.

The technical therapeutic considerations for this kind of psychotherapy are specific and clear-cut. The therapist must encourage the development of a therapeutic alliance and must create an atmosphere where learning can take place. Taking advantage of the prevailing positive transference feelings, staying within the specified focus, and using anxiety-provoking confrontation questions, clarifications, and interpretations, he must strive to avoid getting entangled in pregenital characterological issues, such as passivity, dependence, sadomasochistic or narcissistic features, and acting-out tendencies which are used defensively by the patient and which tend to prolong the treatment.

With attention to both the cognitive and the emotional components, new learning, self-understanding, and problem-solving techniques are systematically taught to the patient so as to bring about a "corrective emotional experience" and a dynamic resolution of the Oedipus complex. Finally, and as soon as evidence is provided in terms of tangible examples that changes are actually taking place, the therapy must come to an end. (pp. xv–xvi)

The book is divided into three sections. Part one describes the initial evaluation of patients for short-term anxiety-provoking psychotherapy, including taking a detailed history of psychological development, reformulating the presenting complaints into a psychodynamic hypothesis, assessing the patient in terms of specific selection criteria, establishing a

dynamic focus for the treatment and a therapeutic contract with the patient, and specifying successful outcome criteria. According to Sifneos, common presenting complaints of good short-term anxiety-provoking psychotherapy candidates include the following: interpersonal difficulties, phobias, anxiety (sometimes in conjunction with a variety of physical symptoms), and mild depressions and obsessive-compulsive problems. The selection criteria for short-term anxiety-provoking psychotherapy patients that are elaborated include 1) a circumscribed chief complaint, 2) evidence of a "meaningful" give-and-take relationship with another person during early childhood, 3) the capacity to relate flexibly to the interviewer and to express feelings freely, 4) psychological sophistication, involving above-average intelligence and psychological-mindedness, and 5) motivation for change rather than for mere symptom relief. A helpful questionnaire synthesizing all important components of the psychiatric evaluation process is presented at the end of part one.

Part two of the book presents detailed discussions and clinical illustrations of the opening, middle, and end phases of treatment. Woven into these discussions are explanations and numerous case examples of specific short-term anxiety-provoking psychotherapy technical issues: the uses of transference and countertransference, especially as they relate to the therapist-parent connection; the importance of staying with the oedipal focus and avoiding complex pregenital characterological issues; and the uses of anxiety-provoking questions, confrontations, and clarifications as well as periodic recapitulations of interpretations to maintain motivation and encourage new learning and problem-solving behaviors in the patient.

Part three includes a discussion of training and supervision issues, a review of early outcome studies and a report of more recent research in short-term anxiety-provoking psychotherapy, and a brief discussion of the use of short-term anxiety-provoking psychotherapy with older patients and those with physical complaints. Two appendixes present detailed case material from the treatments of two patients, a man and a woman.

Sifneos repeatedly emphasizes the confrontation, interpretation, and working through of oedipal conflicts and cautions against the faulty evaluation of "certain pregenital character traits" that complicate, extend, and often produce failure in short-term anxiety-provoking psychotherapy. He notes that recent psychiatric attention seems to have "downgraded" the importance of "universal and formidable" oedipal conflicts in favor of understanding early oral and other pregenital difficulties (pp. 127, 128), a shift Sifneos perceives as being due to therapists' own discomfort with their unresolved or partially resolved oedipal conflicts. If therapists carefully select the appropriate patients and are themselves not too countertransference burdened, Sifneos is optimistic:

We should do all we can to spot these individuals who have a potential to resolve their problems rapidly. One of the difficulties, however, is the incredible speed with which changes can take place in these patients. Psychiatrists who have been trained to believe that psychological reactions take a long time to be modified become suspicious when they see such speedy resolutions and tend to undermine the patient's confidence by implying that they represent a "flight into health" or a "counterphobic reaction," or doubt that the positive results will be maintained. On the contrary, the role of the therapist

should be to encourage such patients to do their own problem solving and not urge them to accept long-term psychotherapy instead. (p. 88)

The strength of this book lies in its clear exposition and rich illustration of selection criteria and effective psychotherapeutic techniques. It can be read profitably both by relatively new therapists, who have not been indoctrinated into the often self-fulfilling dogmas of long-term therapy, and by more experienced clinicians interested in sharpening their skills. Additional useful material about the brief dynamic treatment of oedipal problems can be found in the work of Horner (1) and others (2-5). Sifneos is to be congratulated for contributing a method useful with a certain group of patients and for modeling many of the skills and concepts necessary for treating a broader range of psychological problems. The present edition of *Short-Term Dynamic Psychotherapy*, like its predecessor, takes a respected place in the growing literature on short-term dynamic psychotherapy.

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MICHAEL F. HOYT, PH.D.
DIANE ENOS, PH.D.
Hayward, Calif.

The Psychology of Separation and Loss: Perspectives on Development, Life Transitions, and Clinical Practice, by Jonathan Bloom-Feshbach and Sally Bloom-Feshbach and associates. San Francisco, Jossey-Bass, 1987, 559 pp., \$39.95.

This book contains 16 articles that consider the theoretical and clinical aspects of the psychology of separation and loss comprehensively and in detail. It is divided into three sections: The Role of Separation in Early Development, The Role of Separation in Major Life Transitions, and The Role of Separation in Psychopathology and Psychotherapy.

Part one begins with an article on the role of loss in non-human primates, then considers both psychoanalytic and attachment theories of separation in infancy and early childhood, the further development of a sense of separateness in middle childhood and adolescence, and finally the role of separation in the second half of life. Part two examines the separation aspect of life transitions: entry into nursery school, leaving home as an adolescent, work-related parental absence, cultural migration, divorce, and childhood bereavement. Part three explores the theoretical and clinical bases for psychotherapy of individuals with emotional damage at the "preoedipal" level. A last article takes issue with prevailing views of separation and attachment as being male-biased.

The main points of the book are that 1) separation is both an intrapsychic process and a ubiquitous external event and 2) how successfully the self-representation guided by

the caregivers separates from the object representation in early childhood vitally affects the development of a sense of self, which in turn crucially affects the individual's response to all later life transitions, changes, progressions, and losses. Beyond that, the authors attempt to establish the commonalities seen in three theoretical perspectives: psychoanalysis (both object relations and self-psychology), attachment theory, and developmental psychology. For example, the authors describe the notion of a healthy or competent self as possessing object constancy, self-structure, or secure attachment.

This is a big book in conception and in size. The editors provide concise introductions to each chapter that give the book focus and continuity, and there are bibliographies so extensive that one could use them for independent study. Some of the writing is labored and circumstantial but most is excellent.

Despite the plethora of publications on separation and loss, this book deserves a place as a thoughtful, careful, scholarly bringing together of knowledge from different perspectives. Although some of the material restates the obvious, the book can serve the person experienced in the field as a reference source, while for the newcomer it offers a bonanza.

JAMES F. MASTERSON, M.D.
New York, N.Y.

Handbook of Cognitive Behavioral Therapies, edited by Keith S. Dobson, Ph.D. New York, Guilford Press, 1988, 426 pp., \$35.00.

In a rapidly expanding field such as cognitive psychotherapy, a handbook is an indispensable tool of the clinician. Unfortunately, Dobson's *Handbook of Cognitive Behavioral Therapies* does not live up to the promise of its title. Although the book reviews current major theories of cognitive therapy and approaches to treatment, it is not presented in a form particularly useful for the clinician. A good handbook of cognitive therapy should be organized by clinical syndromes or by patients' presenting problems, with comprehensive analyses of currently available cognitive treatments. It is disappointing that this book is much less ambitious and consequently less useful for the clinician.

Like so many recently edited books on the topic, each chapter constitutes a distinct theoretical point of view within the family of theories of cognitive psychotherapy. In the first chapter Dobson and Block present a brief overview of recent developments in the field of cognitive-behavioral psychology. In the second chapter Segal and Shaw review questionnaires currently available to the cognitive therapist. This review is organized from an information-processing-model perspective and, in general, does not appear to be a useful guide of available cognitively based tests for the practitioner. Chapters three, four, and five present D'Zurilla's problems-solving therapy, a review of self-management therapies by Rehm and Rokke, and a review by Braswell and Kendall of cognitive-behavioral methods used with children. Chapters six, seven, and eight present Ellis's rational-emotive therapy, Beck's cognitive therapy, and Guidano's structural approach to cognitive therapy, respectively. Although these last three chapters at first glance appear to be the most important chapters in this book, very similar chapters appear in other edited books on the topic (1-3) as well as in more complete forms elsewhere (4, 5).

In chapter nine Mahoney lucidly reviews the development of constructivistic cognitive-behavioral theories, which is best represented by Guidano's work, contrasting it to the development of rationalist cognitive-behavioral theories, which are best represented by the works of Ellis and Beck. Unlike the rationalist cognitive approaches, the constructivistic cognitive theories are more closely tied to Bowlby's attachment theory (6) and Kelly's concept of personal constructs (7) than to behavioral theories. Constructivistic cognitive therapists adhere to Weimer's motor theory, which "asserts that humans actively create and construe their personal and social realities" (p. 364). From this point of view, it is not enough for therapists to focus exclusively on conscious, self-defeating, or dysfunctional thoughts in the course of therapy, but they must also explore the underlying personal constructs of the patient.

In the final chapter Dobson speculates on the future of cognitive-behavioral therapy. He predicts that in time cognitive-behavioral theorists will turn their attention to developing a cognitive model of psychopathology in childhood.

For the therapist unfamiliar with the theoretical underpinnings of cognitive psychotherapy, the *Handbook of Cognitive Behavioral Therapies* may be useful as an introduction to the field. However, an applied clinical handbook as a companion to this volume is sorely needed and would fully earn the rather grand label of "handbook."

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JOEL F. MERESMAN, PH.D.
Belmont, Calif.

PSYCHOPHARMACOLOGY

Brain Systems, Disorders, and Psychotropic Drugs, by Heather Ashton. New York, Oxford University Press, 1987, 523 pp., \$85.00.

This book is a comprehensive, clearly written review of current knowledge of brain function and the effects of psychoactive drugs on such function. Heather Ashton, a British psychopharmacologist who is not well-known in the United States, has contributed importantly to the British literature, especially in the fields of drug abuse and benzodiazepine pharmacology. Stimulated by her many years of teaching medical students at the University of Newcastle Upon Tyne, this book has the ambitious goal of integrating the neurobiological basis of normal and abnormal brain function with

the various syndromes of mental illness and then discussing the impact of clinically available psychotropic drugs on brain function and mental illness. Most books that attempt such an integration are multiauthored reviews of research data with little relevance to the clinician. The great strength of this book is the clarity with which the author synthesizes an enormous body of neurobiological as well as psychopharmacological literature in a format that provides an introduction as well as a review of these complex topics for the practicing clinician.

The introductory "overview" chapter defines Ashton's basic vision of brain function. In a lucid writing style, she discusses the complex interactions among various neurotransmitter systems and reminds the reader that a simplistic notion of a single neurotransmitter for a single disease or symptom is highly unlikely. The effect of a neurotransmitter released at a synapse depends on which neurotransmitter system it is operating in (neurotransmitters may operate simultaneously in several functional systems); these different systems may also share overlapping anatomical pathways with multiple backup circuits. There may be several subtypes of receptors for each neurotransmitter, some with opposite functions (e.g., excitatory or inhibitory). Neurotransmitter receptors are dynamic structures whose density and sensitivity undergo adaptive changes, and they may behave differently depending on acute versus chronic alteration in transmitter availability. Each of these concepts is amplified throughout the remaining chapters, providing the basic format for discussions of contemporary neurobiological theory and knowledge.

Somewhat more controversial is the second basic thesis of this book, also stated in the introduction and then used as the organizing principle for the remainder of the volume. Ashton states that all human behavior depends on only three functional systems in the brain: systems for arousal, systems for reward, and systems for learning and memory. Affective and emotional states as well as motivation, perception, love, creativity, etc., are all defined by the complex interaction of these three systems. "Emotional color" such as fear, anxiety, pleasure, and aversion are considered part of a goal-oriented arousal system. Psychiatric disorders are understood as dysfunctions within these systems: anxiety and sleep disorders are considered dysfunctions of arousal systems, drug dependence and chronic pain syndromes as well as depression and mania involve reward and punishment systems, and schizophrenia is an abnormality of integration among all the systems.

Following this overview, the book is organized into three parts, one for each of the functional systems: arousal and sleep, reward and punishment, and learning and memory. Each of these parts, in turn, is separated into three components: an overview of the neurochemistry of the functional system, a discussion of the psychiatric syndromes that may be associated with disorders of these functional systems, and the effect of psychoactive drugs on these systems. Following a discussion of these three basic neurofunctional systems, their disorders, and the impact of drugs on the systems, specific sections are devoted to affective disorders and schizophrenia. Each of these is divided into two subsections: the clinical features and associated neurochemistry and the clinical use of drugs to treat these disorders.

Although the existence of basic neurofunctional systems has been postulated and speculations regarding their importance in human behavior are sometimes included in discussions of brain function, the state of contemporary neurobiological knowledge is hardly sufficient to reduce all human

experience to these three functional brain systems. Furthermore, many clinicians may be somewhat appalled at this rather mechanical and reductionistic view of the complexities of human emotional experience. Ashton is most successful when using these systems to discuss anxiety disorders and when reviewing drug abuse. In discussions of affective disorders and schizophrenia in the latter half of the book, however, Ashton herself seems to place less emphasis on these three organizing neurofunctional systems, and the reader wonders whether the systems as defined are helpful in the treatment of these disorders. It may be that arousal systems are useful for understanding anxiety, reward and punishment systems useful for understanding drug abuse, and learning and memory systems important for understanding cognitive dysfunction, but their importance in understanding major mental illness is still somewhat uncertain. Furthermore, although Ashton emphasizes the interplay of neurotransmitters, neuromodulators, and their many different receptors in the early sections of the book, she seems to shift to a more traditional single-transmitter theory of major mental illness, especially the role of dopamine in schizophrenia. The reader who is promised a more comprehensive neurobiological understanding of these disorders early in the volume is somewhat let down by the standard neurobiological theories that are reviewed in the latter half of the book.

The book is less successful in other areas as well. Although it is comprehensive in scope and contains an enormous bibliography, U.S. readers may be somewhat surprised by Ashton's choice of primary references on which she constructs her neurobiological and pharmacological discussions. Many of the references cited are from the British literature, often from *Lancet* articles or other clinically oriented British journals rather than reports of controlled research studies. Many of the U.S. research references that are cited were published before 1983, and some of the more classic papers have not been considered. To give a single example, the section on sleep and mechanisms of REM stage control does not even mention the pioneering neurobiological studies that have dominated the U.S. literature for the past several years. The reader who is knowledgeable about the current neurobiological literature, therefore, might believe that Professor Ashton is either displaying a notable British chauvinism or selectively citing references that bolster her own vision of neurobiology and psychopharmacology. The author, of course, is entitled to cite the references she chooses, but in a book that serves as a comprehensive integration of several bodies of knowledge, it would have been helpful to have her biases openly stated.

There are other curious omissions from the text. For example, flurazepam is not mentioned in a listing of available benzodiazepines. Since flurazepam is one of the most widely prescribed benzodiazepine hypnotics, this omission is surprising from an author who is an international expert on benzodiazepines. In the section on arousal systems, considerable attention is paid to the possible roles of serotonin (and norepinephrine) in anxiety states, but then in the excellent discussion of γ -aminobutyric acid (GABA) function in clinical anxiety, the relationship among these three neurotransmitters is discussed only in an almost offhand sentence. Since relationships among neurotransmitter functions are the crux of this entire volume, such a brief consideration is disconcerting. In the section on affective disorders, considerable attention is directed toward the concept of presynaptic α_2 supersensitivity in depression, but less is made of the opposite and plausible theory of receptor subsensitivity. The author chooses not to consider ECT, but a discussion of the effects of this treatment on reward and punishment systems

would have been most useful. It is also somewhat surprising to note that there are several typographical errors throughout the text, which is unusual in the high-quality books published by Oxford University Press. Finally, there is no concluding chapter, no grand synthesis supporting her comprehensive vision outlined at the beginning of the volume, and no hopes, encouragement, or suggestions for future research.

How then can this volume be summarized? Its scope, clarity, and organization are superb, and it should be useful to students, psychiatric residents, and clinicians who wish to acquaint themselves with neurobiology and the fundamentals of psychopharmacology without wading through huge multiauthored books of research studies. It is not a book to guide the practicing clinician with specific diagnostic or prescribing information and advice, however. There are no clinical vignettes or case presentations. Nor is this book likely to bring new information to the student or researcher who is already familiar with neurotransmitters and their receptors or with basic principles of psychopharmacology. Professor Ashton is most successful in presenting, in a highly readable and absorbing fashion, a comprehensive but not entirely traditional understanding of the behavioral and clinical consequences of brain function. As a single reference for these purposes, this book is highly recommended.

CARL SALZMAN, M.D.
Boston, Mass.

Antimanics, Anticonvulsants and Other Drugs in Psychiatry: Drugs in Psychiatry, vol. 4, edited by Graham D. Burrows, Trevor R. Norman, and Brian Davies. Amsterdam, Elsevier (New York, Elsevier Scientific Publishing Co., distributor), 1987, 438 pp., \$133.25.

The first three volumes of this series dealt with antidepressants, anxiolytics, and neuroleptics, respectively. Approximately 20% of this volume deals with antimanic agents; the remainder of the text is devoted to a range of topics that are "important in everyday psychiatric practice" but often not included in clinical psychopharmacology textbooks.

The antimanic section contains four chapters. The first is a dated description of lithium pharmacokinetics. The second is primarily a review of data on the efficacy of lithium in the treatment of bipolar illness. The third is a rather limited description of the use of neuroleptics and other agents such as naloxone, reserpine, and clonidine in the treatment of bipolar illness. Interestingly, nothing is mentioned of the value of the calcium channel blocker verapamil as an antimanic agent. Fortunately, Post's chapter regarding the use of carbamazepine in bipolar illness lends some clinical utility to the section.

The second portion of the book deals with anticonvulsant pharmacology. It is hard to imagine that any of the four chapters would be of any value to clinical psychiatrists unless they are treating many patients with seizure disorders. It is worth noting that the issue of the use of anticonvulsants other than carbamazepine in the treatment of bipolar patients apparently was not considered of value to this section of the text.

The third major topic considered is anticholinergic pharmacology and its relationship to clinical psychiatry. The authors consider two relevant issues, anticholinergic drug-induced delirium or intoxication and the effects of anticholinergic drugs on memory. Two chapters are devoted to the pharmacology of β blockers. The first considers the use of

propranolol in the treatment of schizophrenia, and the second examines the use of β blockers in the treatment of anxiety disorders. The next section reviews the mental changes produced by corticosteroids and the relevance of oral-contraceptive-induced mood changes. Then a section on Psychotropic Drugs in Movement Disorders reviews the drug treatment of Tourette's disorder, Huntington's chorea, and Parkinson's disease. The chapters on Tourette's disorder and Huntington's chorea deal with the effects and consequences of pharmacotherapy of these disorders, and the chapter on Parkinson's disease discusses the psychiatric presentation of patients with this disorder. Miscellaneous Use of Psychotropic Drugs contains four excellent reviews of the drug treat-

ment of phobic disorders, alcoholism, dementia, and pain. The last section of the volume, Adverse Drug Effects, contains clinically relevant chapters on drug-induced sexual dysfunction and drug-induced mental disturbances as well as a chapter on compliance.

Overall, as is usually the case in multiauthored texts, the volume is somewhat uneven in its fund of clinically useful information for the practicing psychiatrist. The chapters on antimanics and anticonvulsants are overall cursory reviews with few insights. However, the remaining chapters are perceptive reviews of considerable value to the clinician.

PAUL J. PERRY, PH.D.
Iowa City, Iowa

Reprints of Book Forum reviews are not available.

Letters to the Editor

Influence of Fluoxetine on Plasma Levels of Desipramine

SIR: Fluoxetine was recently approved by the Food and Drug Administration for general use. It is known to act as a specific selective blocker of serotonin uptake and has had few significant side effects (1). I am writing to point out possible interaction effects when fluoxetine is used in combination with the relatively selective noradrenergic tricyclic antidepressant desipramine.

Mr. A entered treatment as a 33-year-old with a 14-year history of depression. His depression showed initial improvement with phenelzine and tranylcypromine, but he relapsed following the death of his father. After other medications (nortriptyline, lithium plus monoamine oxidase inhibitors, bupropion) had been tried, the patient was given a combination of fluoxetine and desipramine. The doses were gradually increased to a maximum of 40 mg/day of fluoxetine and 150 mg/day of desipramine for 5 weeks.

Despite improvement in his depressive symptoms, Mr. A complained of side effects: dry mouth, tinnitus, and, especially, difficulties with memory and alertness. Therefore, at his request, the fluoxetine was discontinued. Blood levels of desipramine were ascertained 2 days, 9 days, and 49 days after discontinuation of fluoxetine while a constant dose of desipramine was maintained. The results indicated blood levels of 938.0 ng/ml, 595.9 ng/ml, and 47.8 ng/ml, respectively. During this time, the patient's dry mouth and tinnitus disappeared and the alertness and memory problems were reduced.

Desipramine levels in this patient dropped off gradually during the initial weeks and then sharply 30 days after discontinuation of fluoxetine. These results are quite in accordance with an influence of fluoxetine on desipramine blood levels, as the half-life of fluoxetine and its major metabolite, norfluoxetine, is known to be 7–9 days. Five half-lives for ridding the body of more than 90% of the drug would thus be 35–45 days.

All psychiatrists should be aware that the combined use of fluoxetine and desipramine may lead to exaggerated blood levels of desipramine, perhaps because of the effect of fluoxetine on liver metabolism, leading to slower breakdown of desipramine.

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PAUL J. GOODNICK, M.D.
Delray Beach, Fla.

Clomipramine-Induced Pseudocyanotic Pigmentation

SIR: Skin pigmentation is a recognized side effect of tricyclic antidepressants (1). However, this side effect has not been reported with clomipramine. We report the case of a patient taking clomipramine who displayed pseudocyanotic pigmentation on areas of her body that were exposed to light.

Ms. A, a 60-year-old housewife, had been treated for 7 years for unipolar depression. During her depressed periods she had been given amitriptyline, imipramine, nortriptyline, and mianserin at effective doses for about 4–6 months each. During her last episode of depressive illness, clomipramine, 75 mg/day, had been given. The dose had later been raised to 100 mg/day. She used the drug at this dose, without visiting her doctor, for 8 months. When she was seen by her psychiatrist, she was not depressed but had pigmentations on the light-exposed areas of her face and hands; these had appeared 7 months earlier and had gradually increased. She denied any past allergy to sunshine. She was not taking any other medication. Her face displayed striking slate-gray, blue-black, and purplish (pseudocyanotic) pigmentations, predominantly involving the cheeks, chin, and nose. The forehead and periorbital skin were much less affected. The mucous membranes and areas not exposed to sunshine were normal. There were no pigmented lesions on the cornea, the lens, and the retina. Lesions very similar to those on the patient's face were visible on the backs of her hands. Results of a physical examination and biochemical investigations, such as CBC, determinations of serum iron level and immunoglobulin concentrations, and protein electrophoresis, were all normal. There was no eosinophilia.

Punch biopsies were taken from the lesions. Microscopic examination revealed liquefactive degeneration in the basal cell layer, mononuclear infiltration around the blood vessels of the epidermis, and extensive deposits of melanin in the upper dermis. Although not specific, these findings suggested a photosensitivity reaction. The drug was discontinued and the patient's condition was followed for another 8 months. The skin discoloration gradually decreased. At the end of the 8 months there were a few light-brown pigmentations on her face only.

The mechanism of photosensitivity as a drug side effect is unclear. It may be related to a cytotoxic photoproduct formed by ultraviolet radiation. This phenomenon is more frequently seen among females and dark-skinned individuals. Estrogens may accelerate the melanogenic effects of the drugs. Photoallergic side effects, which manifest themselves as urticarial maculopapular eruptions or eczematous reactions, occur after a certain incubation period and in patients using even small amounts of the offending agent. A phototoxic reaction can occur in almost any individual, provided there is an adequate concentration of the photosensitizer in

the living epidermis and exposure to a certain band of sunlight. This is not an autoimmune reaction (2). It is generally believed that there is no cross-allergy between different agents, but changing the drug complicates the problem (3).

Our patient, living in a region of western Turkey that is richly endowed with sunlight, had used various antidepressant agents for 7 years. She experienced a phototoxic reaction only when she was using clomipramine, and it virtually disappeared after cessation of the drug. She was not restarted on clomipramine to confirm this side effect.

Phototoxic reactions due to neuroleptic agents, especially phenothiazines, are well-known (4, 5). The appearance of similar pigmentary lesions of the skin and the ocular retina after use of tricyclic antidepressant drugs is not surprising, since these two separate groups of drugs have some similarities. Both chlorpromazine and imipramine have an $\text{NCH}_2\text{CN}_2\text{CH}_2\text{-(CH}_3)_2$ chain. It is interesting to note that clomipramine has even more molecular similarities to chlorpromazine.

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ZELIHA TUNCA, M.D.
MEHMET I. TUNCA, M.D.
AHMET DILSIZ, M.D.
ÜMIT BAYOL, M.D.
MEHMET HANCIOĞLU, M.D.
Izmir, Turkey

Methylphenidate for Cyclosporine-Associated Organic Mood Disorder

SIR: Cyclosporine is an immunosuppressant that is in common use to prevent the rejection of transplanted organs. This drug has been associated with a spectrum of neurotoxic side effects, including organic mental changes. Disorientation, hallucinations, delusions, depression, apathy, inactivity, loss of appetite, agitation, and racing thoughts have been reported (1-3) and may occur at drug levels required for immunosuppression (serum levels of 200-500 $\mu\text{g/liter}$). These symptoms may resolve with stabilization or decrease of serum levels or, less frequently, may progress to more severe neurotoxic effects. However, it may not be possible to decrease or discontinue cyclosporine without substantial risk of organ rejection. We would like to report the successful treatment with methylphenidate of a patient who had a cyclosporine-associated organic mood disorder, depressed type.

Ms. A, a 42-year-old woman, received a single lung transplant. One month after surgery, she was medically stable, and hospital discharge was being considered. However, the staff had noticed that, quite out of character, Ms. A had become inactive and withdrawn and approached

rehabilitative care with hesitancy and lack of interest. During psychiatric assessment, she reported a 2-week history of loss of interest in all activities, mildly depressed mood, anhedonia, loss of energy, loss of appetite, insomnia, and poor concentration. In addition, she reported frustration at being "held down" by lethargy and apathy, which was "not like myself." Results of a cognitive examination were otherwise normal. Neurological examination demonstrated a mild peripheral neuropathy attributed to the cyclosporine. There was no personal or family history of mood disorder, substance abuse, or other psychiatric disorder. The patient had received cyclosporine from the time of the transplantation. Her core symptoms of apathy, lethargy, and loss of appetite were similar to side effects that have been associated with the use of cyclosporine (1, 3). There was no other recognizable medical factor responsible, and the symptoms could not be fully explained as a normal or disordered adjustment process.

Because Ms. A had a right bundle branch block and a speedy recovery would facilitate hospital discharge, methylphenidate, rather than a tricyclic antidepressant, was prescribed as the first choice for treatment. A 5-mg dose was administered at 8:00 a.m. and at noon. From the first day of treatment, the patient reported marked improvement in all symptoms, and full recovery occurred within 4 days. Improvement was sustained and adverse effects did not occur during 4 weeks of treatment at this dose. The drug was then tapered and discontinued without recurrence of the patient's symptoms.

Methylphenidate has been successfully used in depressed, medically ill patients as an alternative to tricyclic antidepressants (4). In particular, apathetic, withdrawn elderly patients may respond to this drug (5). The cyclosporine-associated organic mood syndrome described in this case has complicated the postoperative course of other transplant recipients; however, we have not previously attempted to intervene. This case suggests that methylphenidate may be effective in treating the apathy, lethargy, and loss of appetite which may result from treatment with cyclosporine.

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JOHN L. CRAVEN, M.D., F.R.C.P.(C)
Toronto, Ont., Canada

Evaluation and Treatment of Catatonia

SIR: We recently had the opportunity to evaluate a patient with cerebellar degeneration who presented with catatonic

features. This case reminds us of several important aspects of the evaluation and treatment of catatonia.

Mr. A, a 19-year-old black man, had a 4-month history of progressive withdrawal, weight loss, and mutism. He had recently been demoted at work. Initial evaluation failed to disclose neurological abnormalities other than psychomotor retardation. A psychiatric consultant made a diagnosis of unipolar depression and attempted a trial of nortriptyline. The patient was noncompliant and deteriorated to a state of catatonia. This catatonic state hampered formal examination by a consulting neurologist who interpreted the symptoms as functional, secondary to the patient's grief over the loss of his maternal grandfather from a progressive degeneration.

Mr. A began to refuse food and drink and was hospitalized. The routine assessment was hampered by his severe catatonia. A parenteral dose of lorazepam resulted in improved cooperation and speech. A formal neurologic examination became possible while the patient was under the effects of the lorazepam. The examination revealed scanning speech, ataxia, dysphagia (in the presence of a normal gag reflex), oculoparesis on slow pursuit, and poor rapid alternating movements. The mental status examination did not reveal important depressive features. There was mild paranoid ideation, but no first-rank symptoms were elicited. During the course of the day, the effects of the lorazepam wore off, and Mr. A became catatonic once more. A CT scan of the brain revealed prominent cerebellar and brainstem atrophy. A provisional diagnosis of cerebellar degeneration was made. Because of the pronounced effect of the lorazepam, we began a therapeutic trial of another benzodiazepine, clonazepam. At a dose of 1.5 mg t.i.d., Mr. A has had maximum mobility and is quite engageable. Cerebellar signs are also at a minimum at this dose.

Mr. A's illness offers a reminder of the close association of movement disorder and psychiatric illness (1). It also cautions that there are many organic causes of catatonia; the differential diagnosis includes epilepsy and disorders of the basal ganglia, limbic system, diencephalon, and frontal lobes. Cerebellar degenerations are not typically included, but some share the common features of a wide range of movement and psychiatric symptoms, such as ataxia and dysarthria, dementia, depression, and psychosis (2). The cerebellum has a high density of benzodiazepine receptors (3). One might speculate that Mr. A's cerebellar degeneration reduced the functional activity of γ -aminobutyric acid (GABA). It is not surprising that this cerebellar degeneration presented as catatonia and responded to a GABA agonist such as lorazepam. The use of lorazepam as a sedative-hypnotic during the interview was helpful in achieving a more complete neurological examination. Such a technique can be valuable in the evaluation of catatonia (4). It allows access to the mental state to examine for symptoms of depression or schizophrenia. The neurological examination—otherwise difficult to do—is facilitated by the increased mobility and cooperation of the patient during the sedative-hypnotic interview. It has been suggested that improvement with sedative-hypnotics implies a psychogenic cause for catatonia; this is a generalization (5). There are a number of neurological disorders that respond to lorazepam. The clinician must avoid premature assumptions of psychogenic causes for catatonic symptoms. Initial episodes of major psychiatric illness complicated by mutism and disturbances of mobility

should be thoroughly evaluated with appropriate neuroimaging, including CT and magnetic resonance imaging.

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JEFFREY L. CLOTHIER, M.D.
PEGGY PAZZAGLIA, M.D.
T.W. FREEMAN, M.D.
Houston, Tex.

Treatment of Monosymptomatic Hypochondriacal Psychosis With Pimozide in an AIDS Patient

SIR: It is now well-known that patients with acquired immune deficiency syndrome (AIDS) frequently have psychiatric symptoms. The following is a report of an AIDS patient who experienced delusions of parasitic infestation.

Mr. A was a 39-year-old unmarried man with a history of ethanol and intravenous substance abuse. He had not been drinking and was on methadone maintenance therapy when he was hospitalized with severe anemia and the complaint that worms were present in his mouth, sputum, and vomitus. Frequently examining his mouth with a hand mirror, he would take scrapings of his oral secretions, using a razor blade for more meticulous dissection and examination of the tissues. He placed the scrapings on the mirror to better demonstrate to the staff the "movement of the insects and worms." His past history included hepatitis and alcoholic liver disease, chronic anemia, and colitis. There was no past psychiatric history other than substance abuse. Mr. A was unemployed and described himself as a "loner."

Vital signs and results of thyroid function tests, lumbar puncture, and EEG were all normal. His hematocrit was 22.2% at the time of his admission. Serum chemistry results were unremarkable except for mildly elevated values on liver function tests. A CT scan of the head showed moderate cerebral atrophy without focal lesion.

On mental status examination (after transfusion of three units of packed red blood cells), Mr. A was alert, oriented, and cooperative. His speech was coherent and fluent, his mood was euthymic, and his affect was broad and appropriate to his thought content. Although his concentration was impaired, he could remain at a task without redirection. Immediate recall was intact, but his short- and long-term memory was diminished. Ability to calculate was impaired, and the patient was unable to perform complex sequencing (Trail-Making Test, Part B). There were no

auditory or visual hallucinations. He described a sensation of insects crawling under his skin and would scrape excoriated lesions on his arms with a razor blade in order to dislodge the perceived parasites. He stated the lesions were due in part to sticky secretions from these organisms. The patient also believed that his home was overrun with insects. No other delusions were present. Abstract reasoning, judgment, and insight were otherwise intact.

The patient was started on pimozide, 2 mg/day p.o. After 2 weeks of treatment, Mr. A reported with amazement that he was no longer bothered by any insect infestation. He did experience some cogwheel rigidity and akathisia, which responded to low doses of diazepam.

Monosymptomatic hypochondriacal psychosis consists of a single, fixed delusion in the absence of features of schizophrenia, primary affective disorder, or organic mental disorder. The disorder may be present in either sex at any age and may be of gradual or sudden onset (1, 2). Many patients have prior psychiatric histories, mostly personality or substance abuse problems. Patients with this disorder frequent internists' and dermatologists' offices but rarely accept psychiatric referral (3). If the symptoms are chronic, the prognosis is considered poor.

Pimozide, a diphenylbutylpiperidine neuroleptic, has produced complete or partial improvement in about 80% of cases. Most patients require maintenance pimozide therapy, usually 2–12 mg/day p.o. (1, 4).

Although our patient had some signs of organic mental disorder, it is unclear whether these reflected sequelae of human immunodeficiency virus (HIV) infection or other medical conditions or whether significant preoccupation with the delusion of parasitic infestation had caused diminished attention to cognitive tasks at the time of the initial evaluation. Bishop (5) indicated that organic mental disorder can accompany monosymptomatic hypochondriacal psychosis. Monosymptomatic hypochondriacal psychosis itself may be yet another manifestation of HIV infection. Later mental status examinations did show improvement in our patient, and he continues to be without any delusions of parasitosis.

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VALERIE F. HOLMES, M.D.
Stony Brook, N.Y.

Testing of Persons at Low Risk for AIDS

SIR: I read with interest the article by Steven L. Mahorney, M.D., and Jesse O. Cavenar, Jr., M.D., on the delusion of having AIDS (1). I wish to report another case of this delu-

sion and point out an important issue that physicians must take into account in the evaluation of such patients.

Mr. A, a 34-year-old married white man, was referred to an emergency room after calling his physician about his concern that he had acquired immune deficiency syndrome (AIDS). The referring physician asked that a human immunodeficiency virus (HIV) antibody test be performed. The patient's history and physical examination failed to reveal evidence of AIDS. He agreed to an HIV antibody test but stated that he would kill himself if the test results were positive.

The patient informed a psychiatrist consultant that he was "a lifelong hypochondriac." He reported having become obsessed over the course of several months with the idea that he had AIDS and had passed HIV infection to his wife, his soon-to-be-born child, and his young son. He had taken his son to pediatricians twice weekly for the past several months with trivial complaints. He reported "driving [his] wife crazy" with his obsession. The obsession had developed following a chance sighting of a woman with whom he had had a single sexual encounter about 10 years earlier, when he was engaged to be married to the woman who was now his wife. He denied using drugs and having had blood transfusions or homosexual contacts. His wife and the woman he had seen were the only sexual contacts he had ever had.

In addition to obsessive thoughts, Mr. A experienced overwhelming guilt feelings, convinced that his wife and children were certain to die as a result of his immorality. He was anhedonic and suffered from decreased appetite, weight loss, and disturbed sleep. He was openly skeptical of reassurances that he showed no evidence of AIDS and was unlikely to be infected. He insisted that he would kill himself if he had positive results on the HIV antibody test and that he would not be reassured by a negative test result.

Testing was deferred, and arrangements for psychiatric follow-up were made.

Increasing scientific and media attention has focused in recent months on the accuracy of blood tests to detect HIV infection. Of particular concern is the likelihood of false-positive results, which might be encountered in testing low-risk individuals or groups. Estimates of the probability of a false-positive result range from 1/100,000 (2) to 80/100,000 (3). However, some investigators estimate that, in low-risk groups, up to 90% of all positive test results obtained by commercial laboratories may be falsely positive (3).

In weighing potential costs and benefits before performing an intervention, we must include psychosocial risks in our considerations. This case demonstrates a potentially high cost (suicide) of a false-positive test result for an individual with a low probability of infection. Since a negative test result would not have reassured the patient, the potential benefit of testing was minimal. Thus, a cost-benefit estimation favored not testing.

AIDS phobia is not uncommon even among low-risk individuals (4, 5). Such individuals may be at special risk for catastrophic reactions to false-positive results. The Centers for Disease Control recommends that the test be offered to "all persons who consider themselves at risk," without reference to the individual's true risk status (4). I disagree with this recommendation and urge instead that physicians considering HIV antibody testing in low-risk individuals take

into account the potential psychiatric morbidity which could be associated with false-positive test results.

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BRUCE BLACK, M.D.
Bethesda, Md.

Delusions of Having AIDS

SIR: Steven L. Mahorney, M.D., and Jesse O. Cavenar, Jr., M.D., reported delusions of having acquired immune deficiency syndrome (AIDS) in three patients with affective disorder (1). There have been similar reports in the British literature (2-4). I wish to emphasize how dangerous the delusion is.

Mr. A, a 26-year-old man with a recently diagnosed episode of mania, developed the delusion that he had AIDS. He attempted to kill himself by driving his car into a house but was stopped by a low brick wall; he nonetheless sustained cuts, a fractured humerus, and a fractured femur.

Mr. B, a 74-year-old retired police sergeant, became convinced that he had an infestation of ringworm and then elaborated this into delusions of AIDS. He had symptoms of a major depressive disorder but no relevant medical or psychiatric history and no homosexual or heterosexual contact outside his marriage. He responded initially to pimozide and fluvoxamine but relapsed when he stopped taking them because of side effects.

On admission to the hospital, Mr. B was terrified that he was going to infect other people. For fear of contaminating others, he would only defecate and micturate into a commode by his bed that he could empty. He did not like people to come near him and finally stopped eating and drinking for fear of contaminating the eating utensils. As his physical condition deteriorated, he was given emergency ECT under section 58 of the Mental Health Act and made a prompt and full recovery.

As Drs. Mahorney and Cavenar showed with their cases, it is impossible to convince people with the delusion of having AIDS that they do not have AIDS. However, it is important to understand the implications of the delusion for the individual and to make regular assessments of suicidal intent. O'Brien (5) reported the case of a young man with this delusion who had been referred to a psychiatrist but quietly put his affairs in order and hanged himself before he reached psychiatric attention. It therefore seems important to treat the underlying psychiatric disorder promptly and aggressively.

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JEREMY SEYMOUR, M.B.B.S., D.G.M.
Sheffield, England

Suicidal Tendencies in Women With Human Immunodeficiency Virus Infection

SIR: There have been several recent reports of increased risk of suicidal behavior in patients at various stages of infection with the human immunodeficiency virus (HIV), including those with acquired immune deficiency syndrome (AIDS) (1-4 and unpublished paper by J.R. Rundell, 1988). Marzuk et al. (1) calculated a suicide rate of 680.56 men per 100,000 person-years of follow-up (for ages 20-59), equivalent to a relative risk 66.15 times that of the general population. For California men aged 20-59, the suicide rate for those with AIDS was 436.94/100,000 (2). The suicide attempt rate for HIV-seropositive active-duty Air Force personnel was determined to be 4,535 men per 100,000 person-years of observation (1988 paper by Rundell), equivalent to an increased relative risk for that population of 37.

As described elsewhere (3), the medical center at Lackland Air Force Base is responsible for medically evaluating all U.S. Air Force members worldwide who test positive (by enzyme-linked immunosorbent assay and the Western blot test) for HIV antibodies. Patients receive yearly reevaluations. The rate of infection for female personnel is 0.23/1,000, approximately one-fourth the rate for active-duty men. Women constitute 12.7% of the Air Force personnel. Since 1986, 4.8% of the HIV-seropositive individuals evaluated have been female. All of the data published to date concern men with HIV infection, with no mention of suicidal behavior in similarly infected women. As part of a larger prospective study of psychiatric issues in Air Force members with HIV infection, all women who had been admitted since November 1987 for mandatory medical evaluation (N=15; one patient was also reevaluated) were given the opportunity to participate in an extensive psychiatric evaluation as well. All consented to participate. One patient had AIDS; the remainder were largely asymptomatic, physically healthy women; one was pregnant. The mean length of time that they had known their positive HIV test results was 12.8 months. Their mean age was 26.5 years (range 22-36); 53% were black and 47% were white. None was known to be an abuser of intravenous drugs or to be alcohol dependent.

Consistent with other reports of increased suicidal tendencies in men with HIV infection, we had found that 21% of 89 randomly selected men in our study admitted to suicidal ideation, plans, or attempts at some time since learning of the positive test results. Surprisingly, only 6.7% (N=1) of the 15 women reported suicidal ideation—mild, without plans, at-

tempts, or gestures—in the 13 months since learning of the test results. There have been two known suicides by male personnel with HIV infection (N=711) and none by women (N=34).

Standard psychiatric tests indicate that the ratio of suicide attempts by women to attempts by men is at least 3:1 (5), whereas the ratio of actual suicides is three times higher for men. Our preliminary finding of rare suicidal ideation in women with HIV infection, in contrast to alarmingly high rates of suicidal ideation and suicide attempts in similarly infected men, is puzzling and so far unexplained. It is possible that our female group suffers less from the psychiatric morbidity that generally precedes, or appears in concert with, suicidal tendencies. The prevalence of alcohol abuse and dependence appears to be far lower in women, for example. It has been suggested that homosexuality is a risk factor for suicide (5). The magnitude of the difference in this potentially discriminating factor between our male and female groups is unknown but likely to be great. The interaction between HIV infection and suicidal ideation is complex and poorly understood. We plan to continue our prospective psychiatric studies of those infected with this virus to further characterize the longitudinal biopsychosocial history of HIV infection.

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GEORGE R. BROWN, M.D.
Lackland Air Force Base, Tex.
JAMES R. RUNDELL, M.D.
Bethesda, Md.

Lithium Every Second Day

SIR: Lithium treatment that prevents relapse of manic-depressive disorder will often last for the rest of a patient's life. Long treatment periods emphasize the importance of taking precautions that can reduce side effects; in the case of lithium, this can only be done by reduction of the dosage. We have had good results with respect to renal side effects when lithium intake was decreased from two or three daily doses to one daily dose (1-3). The advantage of one daily dose may be the relatively long period each day in which there is a low lithium concentration, a period in which regenerative processes may occur (e.g., in the kidney).

In order to extend the period of low lithium concentration, for a year we have been treating 10 patients with lithium given every second day. Lithium is given as lithium carbonate, and placebo tablets are given on the days in between; date-marked pillboxes with 31 partitions are used. The patients receive lithium doses which result in 12-hour serum-lithium concentrations between 0.6 and 0.9 mmol/liter and 48-hour concentrations around 0.3 mmol/liter. Patients are

still entering this study, so we do not yet have conclusive results, but so far no relapses have occurred. Furthermore, side effects seem to have lessened. In one patient who during previous normal treatment suffered from edema, lithium intake every second day was followed by disappearance of the edema. In another patient an increased level of serum creatinine was normalized. In still another patient a lithium-induced weight gain decreased. Two patients reported less frequent nocturnal diuresis. One patient, an artist who had stopped painting during conventional lithium therapy, took up his work again after the change to lithium every second day.

Apart from the possibility that lithium given every second day may reduce side effects, another advantage is that the risk of lithium intoxication, and with it the necessity of frequent control of serum lithium concentrations, may diminish.

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HENRIK VEIMER JENSEN, M.D.
KIRSTINE OLAFSSON, M.D.
JOHN ANDERSEN, M.D.
Vordingborg, Denmark
PER PLENGE, PH.D.
ERLING T. MØLLERUP, PH.D.
Copenhagen, Denmark

Cyproheptadine in Movement Disorders

SIR: Cyproheptadine, an antiserotonergic, anticholinergic, sedative antihistaminic agent, was reported to have elicited symptoms of Tourette's disorder in a child—presumably, by its effect on serotonergic systems (1). However, in a non-blind, noncontrolled study, cyproheptadine was also reported to be effective in moderate doses (8-24 mg/day for 2 months) in the treatment of tardive dyskinesia (2). The latter study suggested that cyproheptadine might be expected to ameliorate other involuntary movement disorders in which there is a disturbance of the serotonergic system in the brain. In monkeys with experimentally induced tardive dyskinesia, slight improvement was noted when cyproheptadine was given at higher doses, but not at lower doses (3). A pilot study of five patients given cyproheptadine at a low dose (4 mg b.i.d. for 6 weeks) found no striking improvements in their tardive dyskinesia but suggested a possible antiparkinsonlike effect and suggested that some patients with extrapyramidal movement abnormalities might derive nonspecific benefit from the drug through its sedative effect (4).

In view of these reports, in a nonblind clinical trial with a mixed group of about 40 consenting chronic male outpatients taking neuroleptic and other medications, we added small to moderate doses of cyproheptadine (8-24 mg/day) to the patients' current medications to see if there would be any improvement in tardive dyskinesia and/or extrapyramidal symptoms such as parkinsonism and akathisia. The movement disorders were generally slight to moderate and sec-

ondary to neuroleptic medication. We had tried reducing doses of neuroleptics, and most patients were taking anticholinergic drugs for extrapyramidal symptoms.

Fifteen patients who returned for follow-up reported feeling calmer and sleeping better, but a few also reported depressive feelings. This is paradoxical, as cyproheptadine in a moderate dose (24 mg/day) has been reported to produce a switch from depression to mania, with reduced urinary free cortisol (5); both reactions may be secondary to cyproheptadine's antiserotonergic activity, compatible with the idea that mania occurs when the inhibitory influence of the serotonergic raphe neurons on the hippocampus is removed (5). There was also a mild to moderate improvement in tardive dyskinesia in seven patients, and five patients noted less rigidity and restlessness. A few patients preferred cyproheptadine to benztropine mesylate, which we were able to stop giving to five patients whose tardive dyskinesia and extrapyramidal symptoms had improved. Several patients preferred benztropine mesylate together with cyproheptadine.

The cyproheptadine appeared to have little or no effect on psychotic symptoms. However, we were able to lower doses of neuroleptics for some patients. One patient complained of headaches, and a schizoaffective patient claimed he felt more excited when taking cyproheptadine. Such patients stopped taking cyproheptadine after a few doses.

Improvement in tardive dyskinesia and akathisia was considerable in a few patients; they are still taking this medication. We do not feel that there was an important placebo effect on responders, as these patients' baseline functioning was well known to us. Thus, cyproheptadine at least appears worth a trial in treating the resistant motor side effects of neuroleptics. Further studies are needed; these should be controlled studies and should investigate the effects of higher doses of the drug.

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NORMAN M. BACHER, M.D.
HARVEY A. LEWIS, M.D.
PETER B. FIELD, PH.D.
Baltimore, Md.

PTSD and Suicide Attempts by Adolescents

SIR: Does the *DSM-III-R* definition of posttraumatic stress disorder (PTSD) not also apply to suicide attempts by adolescents? The shift in the concept of PTSD to that of a specific syndrome occurring with or without preexisting and concurrent pathology (1) adds understanding to the phenomenon of adolescent suicide attempts. I have previously described the occurrence of Horowitz's "stress-response syndrome" and

the *DSM-III* concept of PTSD in adolescents who attempt suicide (2).

Many of the changes in the concept describe the symptoms seen in these adolescents even more specifically. Thus, deliberate "efforts to avoid thoughts or feelings associated with the trauma" and "efforts to avoid activities or situations that arouse recollections of the trauma" (*DSM-III-R*) as well as psychogenic amnesia are described by adolescents if they are questioned specifically. Adolescents report anxiety on returning to the scene of a suicide attempt and seeing objects associated with the attempt. Some have anniversary reactions a year afterward, with increased anxiety and reexperiencing of the traumatic event.

The observation in *DSM-III-R* that PTSD is "more severe and longer lasting when the stressor is of human design" would certainly fit the case of a suicide attempt, which is one of the "man-made disasters" frequently seen by psychiatrists.

The more severe the physical threat to life, the more prominent the PTSD syndrome appears, although symptoms are also seen when the attempt was serious in intention but the actual physical injury was not severe. This accords with evidence that an adolescent's suicide attempt is taken more seriously by the adolescent than by those viewing the attempt.

Many questions arise that need further research. Distinguishing preexisting character and affective pathology from PTSD is certainly relevant. There is also the question of how a severe threat to life is determined. Is it a subjective or an objective determination? A requirement of symptoms existing for 1 month would eliminate some instances of adjustment reaction to the suicide attempt but leave the more severe reactions to be diagnosed as PTSD.

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FRANK E. CRUMLEY, M.D.
Dallas, Tex.

Carbamazepine in Panic Disorder

SIR: We have read with great interest several papers dealing with the use of carbamazepine in syndromes related to panic disorder (1, 2). These findings are relevant to proposals for an alternative treatment for this disorder and to speculation about the relationship between the temporal lobe and panic attacks. We would like to report the results of our clinical experience with carbamazepine as a treatment in panic disorder.

Thirty-four patients, 26 female and eight male, 21-56 years old, with diagnoses of panic disorder and panic disorder with agoraphobia (according to *DSM-III-R*), were treated with carbamazepine at a mean dose of 419 mg/day. The period of observation lasted 1 year, and the duration of the treatment was 2-12 months. A final evaluation of the treatment was made on the basis of the variation in number of panic attacks, the degree of avoidance behavior, and adaptive functioning. At least five of the seven psychiatrists on our team—with the exception of the psychiatrist in charge of the case—undertook an evaluation of each case at the end of the observation period. The patient's response, rated either ab-

sent/scarcely or good, was then compared to each of the following variables by one-way analysis of variance: sex, diagnosis, age at first attack, length of illness, age at the beginning of the trial, duration of carbamazepine treatment, and drug dosage.

The results of our investigation showed a good response in 20 patients (58.8%). Significant correlations were found only between response and duration of treatment ($p < 0.02$; good response was correlated with administration of carbamazepine for periods longer than the average of 7.2 months) and between response and drug dose ($p < 0.05$; good response was correlated with doses ranging between 170 and 500 mg/day). The comparisons between response and the other variables did not show any statistical significance. However, it must be pointed out that the response-dose correlation could have been biased by the fact that higher doses probably were less effective because they were given to patients who had failed to respond to lower doses. Our clinical observation that an antiepileptic drug such as carbamazepine could also be effective in the treatment of panic attacks can be included with findings supporting (although indirectly) the hypothesis of a possible role of the temporal lobe (3)—specifically, the parahippocampal gyrus (4, 5)—in the pathogenesis of panic attacks.

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LEONARDO TONDO, M.D.
CATERINA BURRAI, M.D.
LUCIANA SCAMONATTI, M.D.
FRANCESCO TOCCAFONDI, M.D.
ANTONIO PODDIGHE, M.D.
GIANPAOLO MINNAL, M.D.
ANTONIO TUNDO, M.D.
GIANFRANCO FLORIS, M.D.
Cagliari, Italy

Prevalence of Agoraphobia Without Panic in Clinical Settings

SIR: Retention in *DSM-III-R* of the *DSM-III* diagnosis of agoraphobia without panic attacks (i.e., "agoraphobia without history of panic disorder") reflects a belief held by some authorities that this diagnostic category could prove to be a clinically useful complement to the diagnosis of panic disorder with agoraphobia. However, in contrast to the burgeoning literature on panic-based disorders, very little is known about agoraphobic patterns associated with a fear of experiencing forms of sudden incapacitation other than panic. Epidemiologic research (1) suggests that as much as 1.8% of the general population has a condition which meets diagnos-

tic criteria for agoraphobia without panic, but it is still unclear how often this syndrome is encountered by clinicians. The purpose of our report is to provide some preliminary data on the prevalence of agoraphobia without panic in clinical settings.

We recently surveyed a group of practitioners who had a professed interest in anxiety disorders. Respondents were psychiatrists, psychologists, psychiatric social workers, and other mental health professionals from various parts of the United States who were members of the Phobia and Related Anxiety Disorders Special Interest Group. Participants were asked to indicate on a survey postcard the number of patients seen in their clinic during the preceding 12 months who met the *DSM-III* criteria for agoraphobia with or agoraphobia without panic attacks. *DSM-III* categories were used instead of those in *DSM-III-R* because the terminology of the former was considered more familiar at the time and more conducive to contrasting two types of agoraphobia. Group members who had not been actively involved in supervising or providing clinical services to patients with anxiety disorders within the preceding year were asked to refrain from participating in the survey.

Thirty-seven of 93 group members responded to our survey. They reported a total of 932 (mean=25.19, range=0-120) cases of agoraphobia with panic attacks and 61 (mean=1.65, range=0-5) cases of agoraphobia without panic attacks. In other words, approximately 6% of all agoraphobic patients seen by this group of clinicians during the preceding year reported no history of panic attacks as defined by *DSM-III*. Some respondents provided examples of experiences feared by nonpanicking agoraphobic patients; these included limited symptom attacks, migraine headaches, and gastrointestinal distress.

The results of our survey suggest that agoraphobia without panic is relatively uncommon, although not nonexistent, in clinical settings. It is not surprising that this disorder has received so little attention from clinical researchers. Our findings, coupled with results of epidemiologic studies (1), suggest that agoraphobic patients are more likely to seek treatment when they have experienced panic attacks. Indeed, among individuals from the general population who have anxiety disorders, the presence of panic attacks has been one factor associated with seeking professional help (2, 3). Our data suggest that a small percentage of patients have symptoms which meet formal criteria for a diagnosis of agoraphobia without panic. However, little else is currently known about the diagnoses they are assigned.

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C. ALEC POLLARD, PH.D.
SHAEL S. BRONSON, M.D.
MICHAEL R. KENNEY, PH.D.
St. Louis, Mo.

Antecedents of "Spontaneous" Panic Attacks

SIR: I would like to comment on "Prodromal Symptoms in Panic Disorder With Agoraphobia" by Giovanni A. Fava, M.D., and associates (1), in which it was suggested that many individuals with panic disorder/agoraphobia manifest long-standing avoidant patterns before the onset of their first panic attacks. In my practice I see a very large number of individuals with panic disorder and/or agoraphobia. My approach is largely cognitive and behavioral, but unlike the few other practitioners in the city who also see large numbers, I rely less, I believe, on clinical assistants and thus get to know firsthand some of the antecedents, which only gradually come to light.

Without any statistical analysis to back me up, I had already reached the strong conclusion that very often the original, apparently spontaneous panic attack is the culmination of years of avoidances based on various fears. Many of these avoidances have become very refined and subtle, appear natural to the individual (and even part of his or her "character"), and are often highly rationalized. It is only with both increasing exposure to phobic avoidances and some review of their previous behavior that these patients become aware that their avoidances are not natural or inevitable. The entire sequence, however, is not unconscious in the usual psychoanalytic meaning of that word. Rather, it seems that the avoidances have eventually painted the individual into a corner where further avoidances are no longer tenable or the life situation no longer allows them, and panic ensues.

It does not necessarily follow that such apparently spontaneous panic attacks should not be treated with tricyclics merely because the antecedents are detectable, but I would agree that such antecedents are far more common than initial histories indicate, and while some panics still appear "spontaneous," the more detailed the ongoing inquiry, the fewer appear spontaneous.

I thought the article by Dr. Fava and associates was an example of a highly useful and relevant clinical investigation.

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F.W. FURLONG, M.D.
Toronto, Ont., Canada

Addiction to Neuroleptics?

SIR: Like most psychiatrists, I have persisted until recently in telling people that neuroleptics are not "addictive." I had in mind a model of addiction that involves the compulsion to take substances that produce pleasure, euphoria, or sedation. I also had in mind a classic withdrawal syndrome with seizures or other signs of CNS hyperactivity.

As clinicians, many of us have become increasingly aware of the difficulty we encounter in helping patients relinquish these drugs, even when they are made aware of the dangers of long-term use, such as tardive dyskinesia. In addition, there have been reports in the literature of symptoms associated with attempts to discontinue neuroleptic drugs; these include nausea and vomiting, dyskinesias, and dysphoria, sometimes in the form of tardive psychosis (1-3).

Stedman's Medical Dictionary (22nd edition) defines ad-

diction as "habituation to the use of a drug, the deprivation of which gives rise to symptoms of distress, abstinence or withdrawal symptoms, and an irresistible impulse to take the drug again." By this definition, it appears that neuroleptics may produce "withdrawal symptoms" sufficiently severe to compel the individual to continue ingesting the medication. Although the classic model of CNS hyperactivity is not required to fit the definition of addictive, we find this phenomenon in the form of dopamine hyperactivity, the presumed mechanism behind many of the withdrawal symptoms.

Perhaps we should acknowledge that the neuroleptics are potentially addictive and label them as such.

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PETER R. BREGGIN, M.D.
Bethesda, Md.

Should "Depression" Be Dropped the Way "Neurosis" Was?

SIR: Paul Fink, M.D., in his role as President of the American Psychiatric Association, set the theme for this year as "Overcoming Stigma" (1). The upcoming years are also important as we plan the revisions of our nosologies for *DSM-IV* and *ICD-10*. I believe that these two goals are partly linked. With the introduction of *DSM-III*, the term "neurosis" was eliminated (since there was lack of consensus on the definition of the term), and manic-depressive illness became bipolar disorder. The effect of these changes has been to reduce in part the stigma attached to these disorders. Since that time, several public figures have announced that they have bipolar disorder, and the Arkansas appeals court has required a major insurer to reimburse for the disorder as they would for a medical illness. I see two basic reasons for following in the same direction and renaming major depressive disorder.

The first reason is the lack of clarity in the use of the term "depression." Depression is a subjective experience, which patients and others describe in various ways. Everyone experiences periods of depression, but only a few have the illness we call depression. Most of us have successfully treated patients for major depression who have not even complained of depression, particularly agitated or pseudo-demented elderly patients and patients with somatization symptoms. On the other hand, the majority of patients presenting with depressive symptoms do not have major depressive illness. The use of a nonspecific symptom to name a presumably specific syndrome reduces the clarity and meaning of our diagnosis.

The second major reason for the renaming has to do with stigma. Since depression is such a ubiquitous emotion, the general public (our nonpsychiatric colleagues included) believes that people should be able to handle it on their own. This leads to individuals not seeking help or instead pursuing medical investigations of somatic manifestations of the dis-

order (2). One of the objectives of the National Institute of Mental Health depression awareness program is "to change public attitudes about depression so that there is greater acceptance of depression as a disorder rather than a weakness" (3). This would be facilitated by giving the disorder a name other than depression. The problem with our attempts to gain acceptance of depression as a disorder is reflected in our own ambivalence about giving it a name clearly distinct from the ubiquitous normal emotion.

Since bipolar disorder has become a widely accepted term, I am inclined to suggest the label "unipolar disorder" or "unipolar mood disorder." This would be a value-neutral term consistent with our current nosology and not a new term in the affective disorders literature. I believe I have suggested one simple change that we as psychiatrists can make to help destigmatize mental illness while improving the clarity of our nosology.

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NEIL ROBERT LIEBOWITZ, M.D.
Farmington, Conn.

Islamic View of Mental Disorders

SIR: I have recently had occasion to read the chapter on the history of psychiatry in the fourth edition of Kaplan and Sadock's *Comprehensive Textbook of Psychiatry* (1) and should like to call attention to what appears to be a misinterpretation of Moslem views about insanity. The author states, "At the root of . . . [the Arabic] humanitarian attitude was the Moslem belief that the insane person is loved and particularly chosen by God to tell the truth. The difference between insanity and possession was minimal, and the mentally ill were frequently worshipped as saints" (p. 2039).

This generalization is contradictory to Islamic teachings as found in the Koran and the tradition of the prophet Mohammed. The Koran, for example, states, "Do not give money to those with mental disorders, but give them instead food and clothing as these are required, and speak to them gently, saying nice things." In the modern practice of preventive psychiatry, this precept of the Koran is reflected in the establishment of a supportive environment that meets the patients' physical and emotional needs—a central feature of clinical management adumbrated in the moral treatment espoused by Philippe Pinel. Similarly, as in modern psychiatry, the early established Islamic rules for dealing with mental patients emphasized accepting them as human beings and preventing their isolation from their social surroundings—not worshipping them as saints!

Perhaps, therefore, in future editions of the *Textbook*, the sentences I have quoted might be modified to give a more accurate picture of the Islamic view of the nature and treatment of the mentally ill.

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G.H. MOBARAKY, M.D.
Isfahan, Iran

Refinement of the Diagnosis of Schizophreniform Disorder

SIR: According to *DSM-III-R*, the term "schizophreniform disorder" was originally applied to schizophrenia-like psychoses with a good outcome. However, in their fine article "Refining the Diagnosis of Schizophreniform Disorder" (1), Morton Beiser, M.D., and colleagues reported that 70% of the subjects with schizophreniform disorder diagnosed according to the duration-of-symptoms criterion (less than 6 months) were subsequently adjudged to be suffering from schizophrenia, which, by any conventional standard, does not have a good outcome. By demonstrating that the recovered schizophreniform disorder group (30%) had higher *DSM-III* axis V ratings, less affective blunting, and better rapport with the examiner, Dr. Beiser and his colleagues supported the *DSM-III-R* notion that clinical outcome for individual patients with the diagnosis of schizophreniform disorder may be predictable and, in specific instances, good. For the sake of comparison, Dr. Beiser and associates noted that consistent trends in their data suggest that the prognosis for patients with true schizophreniform disorder (the 30% who recovered) is better than that for patients with affective psychosis.

Because of the grave prognosis and stigmata associated with the diagnosis of schizophrenia, might it not be more appropriate to limit the use of the sound-alike term "schizophreniform" to those patients who not only manifest clinical signs and symptoms consistent with the early stages of schizophrenia but also appear most likely to develop the chronic disorder? For schizophreniform patients who present with good prognostic features in the absence of prodromal schizophrenic symptoms, another, more neutral term, e.g., acute anxiety psychosis, might be more appropriate.

In fact, *DSM-III-R* already uses a less perjorative term, brief reactive psychosis, to retrospectively label a symptom constellation strikingly similar to schizophreniform disorder. Brief reactive psychosis differs from schizophreniform disorder only in that 1) it lasts for less than 1 month instead of 6, and 2) in an exception to the general policy of eliminating theoretical and etiological explanations from *DSM-III-R*, it requires a major stress precipitant. Research efforts are needed to assess whether patients who have good-prognosis schizophreniform disorder have more in common with patients who have brief reactive psychosis than with those who have poor-outcome schizophreniform disorder, i.e., schizophrenia. This approach might help to reduce the often noted heterogeneity of patients with schizophreniform disorder as it is presently defined (2).

In the same way, this approach suggests the conceptualization of another category of functional psychotic disorders in addition to those of schizophrenia and depression. Besides the good-prognosis subgroups, true schizophreniform disorder and brief reactive psychosis, this category might include those neurotic patients (with anxiety disorders) who in their most florid manifestations exhibit generic psychotic symptoms. Hirsch and Hollender (3) reported on such a group—

patients with hysterical psychoses—20 years ago. More recently, clinicians have noted psychotic episodes in some patients with war-related chronic posttraumatic stress disorder (PTSD) (4). For example, Mueser and Butler (5) described five patients with combat-related PTSD characterized by prominent auditory hallucinations that were not affected by neuroleptic medications and that were not due to either schizophrenia or an affective disorder. Insel and Akiskal (6), in reviewing the literature and clinical vignettes of yet another anxiety disorder, obsessive-compulsive disorder, described numerous accounts of psychotic symptoms.

Since anxiety is a fundamental human response to stress, it is not reasonable to consider that some of the many instances of acute functional psychotic behavior which readily resolve are in fact due to overwhelming anxiety generated from the interaction of a stressor (extreme and unusual for PTSD or brief reactive psychosis) and one's immediate adaptation to it (exceedingly poor in true schizophreniform disorder and some presentations of anxiety disorders)?

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PATRICK E. CICCONE, M.D.
Gwynedd Valley, Pa.

Adequate Trials of Pharmacotherapy

SIR: The articles by Irene Elkin, Ph.D., and co-workers (1, 2) constitute a good overview of the methodological difficulties encountered in studies comparing the efficacy of psychotherapy and pharmacotherapy in the treatment of depression. We would like to carry the discussion further by commenting on the nature of the pharmacotherapy used in these trials.

We recently reviewed 12 major comparative studies, with emphasis on the adequacy of the pharmacotherapy administered (unpublished paper, 1988). Our findings indicate that the pharmacotherapy may have been inadequate. For example, 1) doses of antidepressants, in imipramine equivalents, were at times as low as 75 mg/day, 2) only three of the 12 studies monitored plasma concentrations of tricyclics, and 3) there seemed to be wide variation in the prescribing physicians' levels of experience, ranging from general practice and training in psychiatry to certification in psychiatry and experience in research.

The most striking finding, however, was that none of the studies made attempts to enhance response to the initial an-

tidepressant by substituting another for it or by adding a potentiating agent such as lithium, tryptophan, or thyroid hormone. These alternative pharmacological approaches are commonly used for patients who have not responded to an adequate first trial of an antidepressant (3). As Dr. Elkin and her associates pointed out, psychopharmacologists have not reached a consensus on the length of an adequate antidepressant trial. However, substitution of one antidepressant for another and addition of potentiating agents are clinical techniques that can be put into practice well within the time required to administer a psychological treatment of 12 weeks or more. The degree of effectiveness of substitution or potentiation techniques is still not conclusively established, but considerable evidence suggests that they permit increases in response rate capable of influencing the results of comparative trials such as the ones reviewed.

Differences in efficacy between two treatments become significant only if both treatments have been administered as well as possible. Provision of the best available treatment in each mode is essential in order to carry out any valid comparison. To reflect this notion, we favor the term "optimization" of treatment. There appears to have been a lack of optimized pharmacotherapy in the comparative trials we reviewed. Future comparative studies of the two treatments should ensure optimization of each. We propose that optimized pharmacotherapy of depression consists of 1) an adequate dose of the antidepressant, 2) intake of the antidepressant for an adequate length of time, 3) determination of plasma concentrations of the antidepressant in cases where the patient does not respond, 4) use of substitution and potentiating techniques for treatment-resistant cases, and 5) an adequate level of expertise in administering antidepressants on the part of the prescribing physician.

A manual recently published by Fawcett et al. (4) showed efforts in this direction. However, it made no mention of monitoring plasma levels of antidepressants and using alternative approaches to treat imipramine nonresponders. We feel that these requirements are essential for optimized treatment and propose their inclusion in future pharmacotherapy standardization manuals.

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GREG METERISSIAN, M.D., F.R.C.P.(C)
JACQUES BRADWEIN, M.D., F.R.C.P.(C)
Montreal, Que., Canada

Combined Fluoxetine and Tricyclic Antidepressants

SIR: Potentiation of the therapeutic effects of tricyclic antidepressants in poorly responding patients is commonly at-

tempted today by adding lithium or thyroid hormone (1). A novel approach—administration of the relatively selective serotonin reuptake inhibitor fluoxetine—to the treatment of two depressed patients already receiving but not responding to tricyclics (in one case, combined with lithium) was reported by D.A. Vaughan, M.D., in a letter to the Editor (2). This addition of fluoxetine was associated with the observation of elevated tricyclic plasma concentrations.

We agree with Dr. Vaughan that a pharmacokinetic interaction between fluoxetine and nortriptyline or desipramine (i.e., inhibition of tricyclic metabolism in the liver by fluoxetine or its metabolites) may have been responsible for the apparent rise in tricyclic levels in these patients after the addition of fluoxetine. However, we wish to append certain caveats and conclusions to this interpretation. First, the analogy to the demonstrated reduced clearance of diazepam by fluoxetine (3) must be viewed with caution. In contrast to the demethylation of benzodiazepines, the major metabolic route of the secondary amine tricyclics is hydroxylation (4); these hepatic pathways are subject to differential influences by competing substrates. A finding of a shift in the ratio of the respective tricyclic hydroxymetabolite to the parent compound would strengthen the argument for diminished tricyclic clearance by fluoxetine. Furthermore, demonstration of the presence in blood of fluoxetine or its metabolites for "several weeks" after dosing, at the time the toxic levels of desipramine were noted in the second case, would more convincingly suggest that fluoxetine was the causative agent. A confounding peak on the chromatogram was appropriately ruled out; we have previously noted in the *Journal* the necessity for clinicians to ascertain the reliability and validity of the laboratory assays with which they work (5).

The clinical implications of these cases go beyond those presented in Dr. Vaughan's letter. Left without comment is a striking inconsistency in the nortriptyline plasma levels of Ms. A. Despite a 40% increase in the daily dose (to 175 mg—more than is usually found necessary for this high-potency compound), the plasma nortriptyline concentration was reported to have risen by only 14.3%. Assuming that the commonly accepted first-order kinetics (4) apply, plasma nortriptyline at the higher dose should have increased to 108 ng/ml, not the 88 ng/ml reported. Other than laboratory error, the most plausible explanation for these changes in tricyclic levels is poor compliance; the supratherapeutic nortriptyline level obtained during fluoxetine treatment might simply reflect more rigorous adherence by the patient to the dosing schedule.

Finally, the rationale for combining two antidepressants is not presented. We are unaware of any data suggesting that fluoxetine is capable of potentiating a tricyclic antidepressant that is not working (1). On the other hand, one would want to first optimize the dose of the initial tricyclic before adding anything. This is illustrated retrospectively in the case of Ms. B, who eventually responded to a "lower dose" of desipramine alone, without fluoxetine. In sum, in our zeal to use the new generation of antidepressants, we should not overlook basic principles.

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MATTHEW V. RUDORFER, M.D.
WILLIAM Z. POTTER, M.D., PH.D.
Bethesda, Md.

Dr. Vaughan Replies

SIR: I appreciate the response of Drs. Rudorfer and Potter to my report on the possible pharmacokinetic interaction between fluoxetine and nortriptyline or desipramine, resulting in a rise in tricyclic antidepressant levels in two patients after fluoxetine was added. I wish to clarify some of the questions they raised concerning my methods and observations.

Assuming that the major metabolic route of the secondary amine tricyclics is hydroxylation, demonstration of a shift in the ratio of tricyclic hydroxymetabolites to the parent compound, or detection of fluoxetine or its metabolites in blood at the time tricyclic levels were determined, would strengthen the argument for diminished tricyclic clearance due to fluoxetine. Such effects could be measured in future systematic study of the suggested interaction.

Concerning our plasma tricyclic assay, we used a high-pressure liquid chromatography method that has been cross-validated by Dorey et al. (1) using that method and gas chromatography.

As noted by Drs. Rudorfer and Potter, Ms. A's nortriptyline level did not appear to increase in direct proportion to the increase in daily dose. This may be attributable to the error inherent in any one reading. These assays have a coefficient of variation of about 15%. The discrepancies between expected and observed values were within this range. Although it is possible that Ms. A did not adhere to the dose increase, her past demonstrated compliance makes this unlikely.

Drs. Rudorfer and Potter question the rationale for prescribing fluoxetine in combination with tricyclics. In both cases my intention was to gradually withdraw these treatment-resistant patients from tricyclics before instituting treatment with fluoxetine alone. In each case the patient "jumped the gun" and began taking fluoxetine before discontinuing the tricyclic as advised.

The statement by Drs. Rudorfer and Potter that Ms. B eventually responded to a lower dose of desipramine is incorrect. Although her side effects gradually resolved, her depression continued.

Interestingly, J.S. Rosenthal (personal communication, 1988) recently observed a synergistic effect of fluoxetine in combination with tricyclics and proposed a mechanism involving the action of serotonin on pretreated synapses. Measurement of plasma levels of tricyclics in patients treated with this combination will provide valuable information regarding a possible pharmacokinetic interaction.

I agree with Drs. Rudorfer and Potter that basic principles should not be overlooked in clinical practice. However, events do not always happen as planned in clinical settings. Such situations may provide alert clinicians with the opportunity to make original observations, which can then be exam-

ined systematically. In this way, clinicians and researchers together can contribute to the expansion of medical knowledge.

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D.A. VAUGHAN, M.D.
Wichita, Kan.

Child Protection Workers' Role in Erroneous Allegations of Child Abuse

SIR: Alayne Yates, M.D., and Tim Musty, A.C.S.W. (1) illustrated four mechanisms that—singly or in combination—may result in erroneous allegations of sexual molestation by preschool children. Professionals involved in this field should remain aware of a fifth mechanism that, regrettably, may still be encountered in child care practice: the production of erroneous allegations through suggestion and persuasion by child protection workers. The following case is illustrative.

When Anne was 3 months old, her parents separated. Her mother, a physician, never accepted the situation. After a bitter 18-month court dispute, the father was granted weekly unsupervised visitation rights. When Anne was 3 years of age, her father rejected her mother's suggestion of a reconciliation, and shortly thereafter the mother made allegations of child sexual abuse against him.

The Child Protection Service accepted the mother's allegations as true. Visitation rights were suspended and an intensive course of therapy for the child was instituted. In 4 weeks Anne attended 12 sessions, lasting from 1 to 2 hours each, in which she was questioned by two child protection workers using anatomically correct dolls. The sessions were videotaped and their contents later revealed in legal proceedings. In the first session, Anne talked happily about her father and denied interference. She had no interest in the dolls and no words for genitalia. As in the second case reported by Dr. Yates and Mr. Musty, the child protection workers interpreted this as resistance and intensified their efforts. Anne was offered sweets and toys if she agreed to various statements. She was told that she and mummy would "get hurt by daddy" if she did not. She was threatened with the loss of her mother: "You wouldn't like mummy to disappear down a big hole, would you?" After 4 weeks Anne was fluent in Latin anatomical terminology. She readily agreed to suggestions that she had suffered full and repeated penetrative vaginal and anal intercourse. It was evident that she believed in these statements, but she was quite unable to amplify them further or produce any description not previously offered by the interviewers. At this point, the results of an initial anogenital examination were reviewed. Expert testimony was obtained to the effect that vaginal and anal penetration had not occurred. Proceedings against the father were dropped.

In this case, the child protection workers adopted without hesitation the mother's apparent conviction that gross sexual abuse had occurred. Her status as a physician may have lent credibility to her story. The child protection workers' determination to find evidence for what they had already decided

must have occurred led to the production of extravagant allegations, which the child clearly believed, but which were directly contradicted by the medical evidence. As this case illustrates, there is a danger that workers in this field will identify so closely with one party that they will share not only the perceptions of that party but also the pathological mechanisms. Erroneous allegations of sexual molestation may then result.

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DAVID V. JAMES, M.B.B.S., M.R.C.PSYCH.
London, England

Dr. Yates Replies

SIR: Dr. James provides a poignant example of a series of events that, unfortunately, can occur in the United States as well as in Great Britain. The parent and the child are abused by a system which may equate success with gathering evidence to prove that abuse occurred. Workers in the field are always poorly paid and undereducated, considering the intricacy of their task. Some workers have biases that impede their ability to be objective, and they may have entered into or have been selected for their positions because of these biases. For instance, a person who was herself sexually abused as a child, who has been a victim in two marriages to abusive husbands, and who has organized a self-help group may apply and be accepted as a Child Protection Service worker because of her background and sensitivity to issues of abuse, without the system assessing whether her biases might impair her objectivity in dealing with these incredibly complex cases.

Many thanks to Dr. James for describing this case. This is an extraordinarily sensitive issue, and we know little about the frequency of such cases or the circumstances under which they occur. Perhaps the publication of examples such as this will encourage agencies to critically examine their policies and procedures.

ALAYNE YATES, M.D.
Tucson, Ariz.

Blood-Injury Phobia

SIR: Since I myself—a psychiatrist—suffered (especially in my younger years) from blood-injury phobia, I would like to offer a comment concerning the article on this subject by Isaac Marks, M.D., F.R.C.Psych. (1). I wholeheartedly agree that the vasovagal collapse in blood-injury phobia seems to be "an adaptive response evolved in circumstances where immobility produced less risk of further injury than did flight" (2). On the basis of my personal experience, I would like to report an interesting observation. As a medical student, I realized that awareness of my own activity, together with the feeling of being in control and in charge of the situation, protected me against vasovagal collapse. I was able to perform venipuncture in my patients without developing the vasovagal reaction. On the other hand, when I was in a passive role, e.g., seeing a venipuncture in a classroom or in a motion picture theater, I might experience sweating, brady-

cardia, and lightheadedness. The only protection in such situations was to put my head as low as possible. This maneuver could not always be done in the presence of others, especially, not when I was sitting in a theater. Self-inflicted pain, as from biting my lips or my tongue or pricking my skin, never modified the reaction once it had started.

Because I am an entomologist by avocation, I have studied and observed various defense mechanisms in insects, for example, mimicry, cryptic behavior, and the immobilization reflex (so-called "thanatosis" or *Totstellreflex*). From this standpoint, as I look for connections between entomology and psychiatry (3-5), blood-injury phobia appears to me to be an archaic protective and "deceptive" mechanism. It is actually an adjustment to the anticipation of real danger resulting from blood loss. The change of the color of the face—the pallor—is a signal to the predator, a kind of mimicry or "chameleon-like" cryptic behavior via identification. When this is connected with fainting, it is an imitation of lifelessness. This could be of some importance in a real battle, even in our century. In cases where this deceptive behavior does not prevent or avoid a physical injury, when the injury does occur, the organism may already be in a condition of lowered blood pressure, thereby possibly decreasing the intensity of bleeding and its consequences.

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GEORGE O. KRIZEK, M.D.
Washington, D.C.

SIR: The article "Blood-Injury Phobia: A Review" presented a scholarly combination of interesting clinical observations, epidemiologic findings, treatment techniques, ethological and physiologic comparisons, and etiological speculations. I would like to add one further speculation. In considering possible advantages for the evolution of such a disorder, I suggest that a vasovagal reflex drop in heart rate and blood pressure at the sight of blood would produce a significant survival benefit: decreased blood loss after injury. If the opposite response occurred, an arterial wound could rapidly produce fatal loss of blood. For the period immediately following such injury, a drop in pressure and heart rate would facilitate other physiologic mechanisms to stop blood loss.

ALLEN Y. TIEN, M.D.
Baltimore, Md.

Dr. Marks Replies

SIR: It is certainly possible that vasovagal syncope at the sight of blood could have some survival value when people suffer blood loss from injury. This factor could have

contributed to its evolution, especially since hominids became bipedal.

ISAAC MARKS, M.D., F.R.C.PSYCH.
London, England

Role of Clinical Skill in Maintaining a Private Practice

SIR: In their article "How to Survive in the Private Practice of Psychiatry" (1), Steven S. Sharfstein, M.D., and Allan Beigel, M.D., failed to address a vital dimension in their comments on the practice of psychoanalytically oriented psychotherapy and psychoanalysis. I agree that there are now economic considerations which make the maintenance of such a practice more difficult than it was in the past, but the role of clinical skill cannot be overlooked.

The work of intensive psychotherapy and analysis requires of the therapist an ability to identify and empathize with the intrapsychic experience of a conflicted and pained patient. While this brief statement does not do justice to a very complex subject, it at least allows me to emphasize that therapists must be constantly able and willing to access their own unconscious processes as they purposefully enter a regressed mental state (2). This is an extremely difficult skill to learn and a hard one to maintain.

In "Analysis Terminable and Interminable" (3), Freud recognized this and called analysis an "impossible profession" (p. 248) because of the "constant preoccupation with all the repressed material which struggles for freedom in the human mind . . . [which] stir[s] up in the analyst as well all the instinctual demands which he is otherwise able to keep under suppression" (p. 249).

Thus, if practitioners of long-term psychotherapy or analysis find that their practice of those modalities dwindles, they might explore their own intrapsychic lives, because there may lie a part of the explanation. Indeed, their own resistances against dealing with mental processes may be driving their patients away. For example, a potential source of long-term psychotherapy patients and analysts is the pool of individuals who come in crisis, desiring brief psychotherapy. Often, these individuals suffer from profound neurotic conflict and fundamental personality disorder but employ mechanisms of defense in the service of ignoring their psychological difficulties, before and after a crisis. The therapist who is resistant to recognizing the mechanisms of defense will do such a patient a disservice by failing to interpret those resistances (4). Then, the patient will surely take flight and lose the opportunity for necessary personality change.

Freud had some suggestions that are relevant here, because they will assist the therapist in acquiring and maintaining the skills needed to build and sustain a long-term psychotherapy practice: have a personal analysis; practice self-analysis in a disciplined way; consider periodic reanalysis (3, pp. 248-249). In addition, periodic supervision with senior psychoanalysts and formal psychoanalytic training should be considered, even if one is primarily interested in long-term psychotherapy. These are all vehicles that enhance one's ability to work effectively with unconscious processes.

To reiterate, those who find themselves unable to build a long-term psychotherapy or analytic practice or retain patients who would best be served by such treatments should look inward; a lack or erosion of skill may be responsible. Those of us who study the nature of contemporary psychiatric practice, too, should not ignore the influence of the practitioner's competence.

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STEPHEN M. SONNENBERG, M.D.
Washington, D.C.

Drs. Sharfstein and Beigel Reply

SIR: We appreciate the reminder from Dr. Sonnenberg that long-term work with difficult patients requires extraordinary clinical skill as well as devotion to this type of work. Our article, however, underscored the impact of the real world of economic constraints and reimbursement rules. Since most patients cannot afford to pay out-of-pocket for intensive outpatient treatment, many clinicians must adapt their clinical skills to these financial realities and must be able to perform a variety of other functions for which they will be remunerated. Fortunately, today psychiatrists have more available in their "black bag" than they did just 20 years ago. The variety of short-term psychotherapies and the expanding effectiveness of psychopharmacology complement psychoanalytically oriented training and skills and increase the ability to sustain a private practice.

STEVEN S. SHARFSTEIN, M.D.
Baltimore, Md.
ALLAN BEIGEL, M.D.
Tucson, Ariz.

Early Interest in the Idiot Savant

SIR: Darold A. Treffert, M.D. (1) presented an exhaustive review of the idiot savant syndrome and its scientific discussion, beginning with E. Seguin in 1866 (2). However, *Gnothi Sauton*, the first journal of empirical psychology in the German language, which began publication almost 100 years earlier (3), had already quoted the case of a prodigious savant that was taken from the *Gentleman* magazine, February 1751:

In the year 1751 there lived a man, called Jedediah Buxton, in the village of Elmton near Chesterfield in Derbyshire. He was 50 years old. His education had been so poor that he could not even write his name. . . . He was capable of swiftly performing the most complicated multiplications and divisions in his mind. The most remarkable calculation human memory ever achieved was his multiplication of the following 39-digit number by itself: 725 958 238 096 074 007 868 531 656 993 638 851 106. After 3½ months, he presented the following 78-digit number. . . . He was able to correctly continue his calculations after many months, exactly where he had been interrupted, and he could repeat the longest numbers backwards and forwards. (3, vol 5, part 2, 1787)

The German translation of this report gives a detailed account of the "extraordinary memory" of Jedediah Buxton, the poor farmhand.

We believe that this case deserves some interest, because it shows not only the early fascination with and recognition of the savant syndrome but also the early international contacts among more or less scholarly journals.

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J. FOERSTL, M.D.
Mannheim, Federal Republic of Germany

Dr. Treffert Replies

SIR: I did include a reference to Jedediah Buxton as a lightning calculator in my review article on the idiot savant, although I did not use the specific reference Dr. Foerstl now kindly brings to my attention. I am looking forward to reviewing this 1787 article in the journal *Gnothi Sauton* to see if it provides any further information regarding Buxton's handicaps, along with his mathematical prowess, since there is some dispute whether Buxton's handicap was mere illiteracy or whether, as suggested in the reference I used (1), mental retardation also existed. Dr. Foerstl correctly points out that prodigious savants were described before this past century; however, the term "idiot savant" to describe these persons has been in use only since about 1887 (2).

My review article has elicited a worldwide response, with hundreds of contacts in over 25 countries, bringing to my attention additional references not otherwise easily traced, such as this one noted by Dr. Foerstl, and also providing new savant cases. Making these contacts and learning about new cases was one of the purposes of the review article; Dr. Foerstl's contribution is an example of such useful discovery of additional information about this (until now) relatively obscure but important topic.

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DAROLD A. TREFFERT, M.D.
Fond du Lac, Wis.

Criticisms of DSM-III-R

SIR: In a recent book review in the *Journal*, Arnold M. Cooper, M.D., and Robert Michels, M.D. (1) provided a thoughtful review of *DSM-III-R*. However, we feel that it is important to correct certain misconceptions. For example, they suggested that the potential misuse of the self-defeating personality disorder diagnosis is "irrelevant to the construc-

tion of a diagnostic entity" and questioned whether we should have had a meeting with the opponents of the diagnosis. They argued that this involvement was allowing politics to tarnish a scientific issue and worried that "the precedent of giving special interest groups a voice in the definition of psychiatric illnesses will make it difficult to exclude them from the process in the future." However, it is not correct to say that the opponents of the diagnosis "did not deny the existence of the disorder." They were, in fact, more concerned with the question of an invalid diagnosis than with the misuse of a valid diagnosis. The misdiagnosis of women in abusive relationships could result in minimizing the contribution of environmental factors to the pathologic behavior. This is clearly a clinical rather than a political problem, and it was just as appropriate and useful to meet with these opponents of the diagnosis as it was to meet with proponents of the hypothesis that self-defeating personality disorder would be a misdiagnosis of an affective disorder. Representatives of both positions attended the meeting, and from their input a number of useful revisions were implemented, including the addition of the two exclusion criteria. A debate over scientific and clinical issues can at times become political (2), but that does not make the issues less scientifically or clinically meaningful.

Drs. Cooper and Michels also regret the exclusion of psychodynamic concepts. They contrasted the criteria for self-defeating personality disorder with the statement in *DSM-III-R* that the name was changed from masochistic to self-defeating "to avoid the historic association of the term . . . with older psychoanalytic views of female sexuality and the implication that a person with the disorder derives unconscious pleasure from suffering." They suggested that this is an "apparent contradiction," but the contradiction is not apparent to us. Their assumption that persons who exhibit the behavior derive unconscious pleasure from suffering was in fact the reason the name was changed. It was not changed because masochism "carries too much emotional baggage and might be especially offensive to women." It was changed for the reasons we have just stated. Drs. Cooper and Michels made the precise error we were trying to avoid: ignoring the fact that there are many other etiological models for this behavior pattern, including biogenetic (e.g., a depressive temperament), cognitive (e.g., learned helplessness and pathological cognitive schemas), interpersonal, and social learning (3, 4).

Drs. Cooper and Michels lamented the absence of a comprehensive organizing system (presumably, a psychodynamic) that would make *DSM-III* easier to teach. We share their regret that the current state of our knowledge prevents such a model from being included. We also regret that students at times "approach their patients with the primary goal of establishing diagnostic certainty . . . at the expense of curiosity about the patient," but this does not suggest an inadequacy of the manual. The fact that a student ignores the caution that a "*DSM-III-R* diagnosis represents only an initial step in a comprehensive evaluation" is a problem in the education of the student and not in the development of the diagnostic manual. Contrary to the experiences of Drs. Cooper and Michels, we have found *DSM-III-R* to be very stimulating and helpful in training because it encourages comprehensive, reliable, and empirically validated diagnosis, and its atheoretical emphasis is helpful in developing an eclectic consideration of alternative models of etiology and treatment.

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THOMAS A. WIDIGER, PH.D.
ROBERT L. SPITZER, M.D.
New York, N.Y.

Drs. Michels and Cooper Reply

SIR: Drs. Widiger and Spitzer make four points, which we will address in turn.

1. They found our review thoughtful. We appreciate their judgment. As we indicated in the review, we found *DSM-III-R* thoughtful.

2. They differ with our concern about the dangers of politicizing the process of developing a nosology. They argue that they were correct to invite critics who challenged the validity of a category to participate in the discussion of it. We fully agree. The issue is whether critics who recognize the existence of a disorder and have only nonscientific, political objections to its inclusion were appropriate participants. We think not and were critical that persons fitting that description were at the meeting. We believe that the decision-making process should focus on whether an entity exists and should exclude those whose interest is only in the political consequences of ignoring or recognizing it.

3. Drs. Widiger and Spitzer find no contradiction in avoiding the notion of "derives unconscious pleasure from suffering" while embracing the description of "undermine(s) pleasurable experiences, . . . is drawn to situations or relationships in which he or she will suffer, and prevent[s] others from helping him or her." Perhaps they are correct. However, the important point is not unconscious "pleasure" but unconscious motivation. We made the generally accepted clinical assumption that masochistic patients are usually unaware of their active search for pain, that is, in the language of most American psychiatrists, that most masochistic behaviors are unconsciously motivated. We think it would have been useful to include this observation in the description.

4. Drs. Widiger and Spitzer share our belief that students should be taught that making a diagnosis is only one step in evaluating a patient and constructing a formulation. We agree with them and stated in our review that the fault lies not in *DSM-III-R* but, rather, with the seductive appeal to educators of its "aura of definitiveness to which it does not itself lay claim."

We close this letter, as we did our review, by referring to the "enormous contribution" of the creators of *DSM-III-R*, "for which the profession owes them honor and gratitude."

ROBERT MICHELS, M.D.
ARNOLD M. COOPER, M.D.
New York, N.Y.

Relationship Between Anxiety and Depression

SIR: Bernard D. Beitman, M.D., and Lyle Clark, M.D., made several interesting points in their letter to the Editor (1), in which they used the term "the inadvertent imipramine challenge test" to describe the experiences of their panic disorder patients who manifested increasing panic attacks after initial treatment with too high a dose of imipramine. Several authors have reported similar adverse experiences. For example, in a recent comprehensive study, Pohl et al. (2) retrospectively noted an acute syndrome of jitteriness, shakiness, increased anxiety, and insomnia in substantial numbers of panic disorder patients treated with low doses of desipramine or imipramine. Sixteen (64%) of 25 desipramine-treated patients and 26 (22%) of 116 imipramine-treated patients experienced the jitteriness syndrome, which in most instances occurred within 1 week.

In a previous letter (3), I suggested that Charney et al.'s (4) conceptual model of panic anxiety, i.e., noradrenergic hyperactivity in conjunction with a dysfunctional α_2 -adrenergic autoreceptor, could explain the propensity of tricyclic antidepressants (which acutely block the presynaptic uptake of amines) to precipitate symptoms like those from amphetamines in panic disorder patients. Drs. Beitman and Clark noted that the antipanic activity of imipramine appears to be preceded by a period of time in which panic attacks may be triggered in the patient. Postsynaptic receptor adaptation, a chronic effect of tricyclics, may explain the cessation of these "panic" symptoms with continued treatment.

Drs. Beitman and Clark briefly cited the complex relationship between panic disorder and depression. Their case report of a patient with major depression who experienced a herald panic attack after initial treatment with imipramine is consistent with such a relationship. However, a putative relationship between general anxiety (irrespective of depression) and panic disorder may also be relevant. Roy-Byrne and Uhde (5) cited a number of reports which suggest that high levels of baseline anxiety may be related to both spontaneous and drug-induced panic attacks. Yeragani et al. (6) recently demonstrated that preinfusion (baseline) anxiety appears to contribute to the likelihood of having panic anxiety during a provocative infusion of lactate and isoproterenol. Although these authors concluded that the role of anxiety is small relative to that of the pharmacologic agents per se, they felt that the anxiety may represent an early phase of panic attack or may be a nonspecific condition that increases the vulnerability to provocative infusions. It would be interesting to ascertain the general level of anxiety of the patient in the case reported by Drs. Beitman and Clark. Unfortunately, baseline anxiety data were not available on 17 additional patients of Pohl et al. (2) who had major depressive episodes in the absence of panic disorder and none of whom manifested the jitteriness syndrome.

In addition to lactate and isoproterenol, many pharmacologic agents, including alcohol, nicotine, marijuana, sympathomimetics, and cocaine, have been implicated in the provocation of panic. General levels of anxiety may play a role in lowering the threshold for inducing panic in the presence of these agents (5). Moreover, if the jitteriness syndrome and other adverse effects like those of stimulants do indeed overlap with panic attacks, then acute presynaptic uptake blockers such as imipramine may well have to be added to the growing list of pharmaceutical provokers of panic.

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PATRICK E. CICCONE, M.D.
Gwynedd Valley, Pa.

Drs. Beitman and Clark Reply

SIR: Dr. Ciccone has offered several very interesting comments on the relationship between anxiety and depression in response to our report of a patient with major depression and no history of panic disorder who had a panic attack after a few days of imipramine treatment. He suggests that the jitteriness syndrome may have a pharmacologic and diagnostic basis in both a dysfunctional α_2 -adrenergic autoreceptor and generalized anxiety. While our patient did not have generalized anxiety disorder, we would add that a cognitive factor may also have played a role in the emergence of panic in this patient. Some evidence strongly suggests that panic is a phobic response to interoceptive stimuli (1). In regard to the jitteriness syndrome, some patients may react phobically with catastrophic thinking ("I have a terrible disease. I'm going to die. No one can help me."). We believe it is important to consider both mind and brain in the etiology of panic attacks. Some attacks will be largely from the mind; others will be largely from the brain (e.g., nocturnal attacks); many will show contributions from each side of the now-melting Cartesian dualism.

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BERNARD D. BEITMAN, M.D.
LYLE CLARK, M.D.
Columbia, Mo.

State Versus Trait in Mental Disorders

SIR: Andrew E. Skodol, M.D., and associates provided interesting longitudinal data on *DSM-III-R* personality measurement (1). In their section on directions for future research, they suggested that a formal study on the effect of depressed or anxious state on *DSM-III-R* personality disorders should be performed. This letter is to inform interested persons that I have proceeded beyond my work on the effect of state on non-*DSM-III* personality variables (2, 3) and have published relevant data on the effect of state anxiety

and depression on *DSM-III* axis II measures (4, 5). Although I used *DSM-III* and not *DSM-III-R* measures, these articles are probably still relevant and of interest.

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JAMES REICH, M.D., M.P.H.
Brookline, Mass.

Drs. Skodol and Oldham Reply

SIR: We thank Dr. Reich for bringing his articles to our attention. Determining whether certain personality characteristics or syndromes are independent of a patient's acute axis I mental disorder has important implications for consideration of these traits as predisposing risk factors. Actually, neither of Dr. Reich's two papers describing assessments based on *DSM-III* criteria (references 4 and 5 in his letter) is a true test of the hypothesis that *DSM-III* personality disorders may be state dependent; such a study would require that the same group of patients be diagnosed first during an acute episode of illness (e.g., depressive or anxiety disorder), reassessed after the acute symptoms have resolved, and compared to suitable control subjects who have not had the illness. A longitudinal design was used by Dr. Reich and his associates in their 1986 paper (reference 2 in his letter), which showed that anxiety caused distortions in the measurement of certain nondiagnostic personality characteristics. Control subjects were used (reference 3 in his letter) to show that in both the ill and recovered state, the personalities of both depressed and panic patients were less "healthy" than those of "normal" persons.

Complicating matters, however, even in longitudinal tests of state versus trait, is the fact that interpretation of findings suggesting state dependence is more straightforward than interpretation of findings suggesting state independence when the prospective study begins with a sample of identified cases. If scores that are elevated on a measure during an episode of illness do not improve when the patient no longer has prominent symptoms of depression or anxiety, it is not possible to conclude whether the elevated scores represent a true measure of antecedent personality or whether the episode of illness caused a lasting alteration in personality. A definitive test would require a prospectively identified, pre-morbid cohort who were tested, followed into a first episode of an axis I disorder and retested, and then tested a third time when they again recovered (1). In light of such a formidable design for an adequate test, it is no wonder that the state-trait controversy continues.

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ANDREW E. SKODOL, M.D.
JOHN M. OLDHAM, M.D.
New York, N.Y.

Plasma Dexamethasone Levels and Disagreement Between the DST and Other Markers of HPA Axis Function

SIR: In their article "HPA Axis Abnormalities in Depressed Patients With Normal Response to the DST" (1), William Meller, M.D., and associates may have overlooked an important variable on the dexamethasone suppression test (DST) side of the equation that could explain the disagreement between the DST and two other challenge tests of hypothalamic-pituitary-adrenal (HPA) axis function (arginine vasopressin and insulin-induced hypoglycemia). The authors failed to take into account the importance of plasma dexamethasone levels in cortisol response, as reported by ourselves and others (2-4). There is wide variability in plasma dexamethasone levels following the standard 1-mg oral dose, with up to one-third of patients failing to achieve adequate levels (2, 4). Low levels of dexamethasone may result in false-positive test results, while high levels of dexamethasone may be associated with abnormal suppressibility of cortisol, producing false-negative results (2).

Using a two-dose (0.5 mg and 1 mg) DST procedure, we have found a number of patients with high plasma levels of dexamethasone (>4 nmol/liter at 4:00 p.m.) who were mis-typed as cortisol suppressors following a 1-mg test, whereas nonsuppression occurred after a 0.5-mg test which achieved plasma dexamethasone levels within an appropriate range or window (2-4 nmol/liter at 4:00 p.m.) (5). Therefore, variability in plasma dexamethasone could have been responsible for the poor association between a normal response to the DST and an abnormal response to the other HPA axis markers in the patients reported on by Dr. Meller and colleagues (1).

We feel that without measuring plasma dexamethasone in their patients, Dr. Meller and associates are not justified at this time in stating that the DST is not a sensitive marker of HPA-axis function. A repetition of the study, including non-depressed psychiatric control subjects and measuring plasma dexamethasone, would be useful to assess the similarities between the DST and other neuroendocrine markers of HPA-axis function. If the two tests were then shown to reflect different HPA abnormalities, the addition of the arginine vasopressin test to the DST could have potential clinical utility.

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GLENN E. HUNT, M.S.C.
GORDON F.S. JOHNSON, M.D.
Sydney, Australia

Dr. Meller and Associates Reply

SIR: We thank Mr. Hunt and Dr. Johnson for their informed comments on our recent article. We agree that plasma dexamethasone levels may play an important role in patients' response to the DST, and measurements of plasma dexamethasone may well enable researchers to improve the sensitivity of the DST.

The purpose of our project, however, was to examine the lack of sensitivity associated with the standard DST, as it is commonly used in research and even in clinical practice. In fact, most published research on neuroendocrine function that uses the DST does not include plasma dexamethasone levels. Work done by Mr. Hunt and Dr. Johnson, as well as other studies cited in their letter, suggests that dexamethasone bioavailability and plasma levels may be important variables to consider in future research using the DST to evaluate the HPA axis.

It should be noted, however, that even if the sensitivity of the DST can be improved significantly, other tests of neuroendocrine function, such as corticotropin-releasing hormone challenge, will be necessary if pathophysiologic correlates are to be drawn. Dexamethasone may have several target organs, e.g., the adrenals, the pituitary, and the hypothalamus, and therefore the ability of the DST to help localize pathology is limited. Nevertheless, we agree that determining dexamethasone levels may represent an important improvement to the standard DST.

WILLIAM MELLER, M.D.
ROGER G. KATHOL, M.D.
RICHARD S. JAECKLE, M.D.
PATRICIA GRAMBSCH, PH.D.
JUAN F. LOPEZ, M.D.
Iowa City, Iowa

"Somatization" of Psychiatric Disorders

SIR: I would like to thank Z.J. Lipowski, M.D., for his important, timely, and cogent review of somatization (1). Somatization as a syndrome, symptom, or cognitive/defensive style has long been a fascinating and vexing phenomenon both theoretically and clinically.

While reading this article, I could not help thinking of several patients I have recently seen who demonstrate a phenomenon that, I think, is related to somatization—a phenomenon that is of immediate concern to clinical psychiatrists and is at least partly iatrogenic. I am referring to what I call the "somatization" of psychiatric disorders: patients reporting that they have disorders of neurotransmitter function or metabolism or saying that their brain chemistry is "off" when they mean that they are depressed or sad or anxious. These patients usually either have read a newspaper report about advances in biological psychiatry or have been

told by a treating physician that they suffer from a biologically based aberration of their brain chemistry that is the cause of their psychiatric symptoms.

This level of somatic explanation has several effects and functions. On the positive side, it helps patients to lessen the stigma of mental illness and to allay the guilt that many people experience in relation to their psychiatric symptoms (see Dr. Lipowski's discussion of etiologic factors). But, as with somatization disorders, this level of explanation allows people to disown their experiences and emotions. It also encourages a kind of therapeutic magic ("Take this pill and all will be solved") and psychotherapeutic nihilism ("What's the point of talking about how this disorder affects my life and how my life affects my disorder? It's all a matter of circuitry"). This discourages patients from taking part in cognitive, interpersonal, and psychodynamic therapies that may help them to solve and/or better cope with their difficulties. It also, unfortunately, encourages some colleagues to ignore important facets of patients' histories as irrelevant to treatment.

I do not mean to belittle recent advances in biological psychiatry. These advances have certainly enriched our understanding of psychiatric illness and opened new therapeutic possibilities for the treatment of our patients. But we should not make the error of the somatizer who blurs observation ("I have a pain") with causal explanation ("It must be cancer"). Observations of response to pharmacologic agents or PET scan variations in psychiatric disorders have not proven causality and certainly do not rule out the importance of appreciating social, historical, and environmental factors in the treatment of our patients.

Just as in treating somatizing patients we need to remain constantly aware of the emotional issues that are being expressed through physical symbols, we also need to remain aware of and attempt to keep our patients aware of the emotional components of their illnesses and their lives. The somatic explanation may be easier and feel better, but some of the emotional life of our work is lost in the process of somatizing psychiatry.

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VICTOR SCHWARTZ, M.D.
New York, N.Y.

Dr. Lipowski Replies

SIR: I appreciate Dr. Schwartz's thoughtful comments on my article and fully agree with their tenor. It is an interesting coincidence that I addressed some of the same issues in a recent lecture presented at the annual meeting of the Canadian Psychiatric Association (1); I take the liberty of quoting from it: "Another current fad is to tell patients that they suffer from a chemical imbalance in the brain. The explanatory power of this statement is of about the same order as if you said to the patient, 'You're alive.' It confuses the distinction between etiology and correlation, and cause and mechanism, a common confusion in our field. It gives the patient a misleading impression that his or her imbalance is the cause of his or her illness, that it needs to be fixed by purely chemical means, that psychotherapy is useless, and that personal efforts and responsibility have no part to play in getting better."

As Dr. Schwartz rightly indicates, this doctor-inspired "somatization" of a patient's psychological problem reflects the ascending biological reductionism in our field, or what I, among others (2), refer to as "mindless psychiatry." This reductionistic tendency is a far cry from Adolf Meyer's (3) insistence that the special sphere of a psychiatrist's work is the study of the *patient as a person*. And a person cannot be equated with his or her brain.

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3. Meyer A: Progress in teaching psychiatry. *JAMA* 1917; 69: 861-863

Z.J. LIPOWSKI, M.D., F.R.C.P.(C)
Toronto, Ont., Canada

Efficacy of Psychoanalysis and Psychoanalytically Oriented Psychotherapy

SIR: Dr. Paul Fink's response to the Presidential address (1) repeated the statement made by Dr. Alan Stone that I regard "all psychoanalysis . . . [as] malpractice because there . . . [are] no good efficacy studies of the procedure" (1). I have never made such a statement. I do not hold this view. It is important to clarify my position and, I hope, shift the discussion from its current emphasis on an individual's views to consideration of the complex problems that confront us. The current dispute derives in large part from the case of *Osheroff v. Chestnut Lodge*.

The patient was hospitalized at Chestnut Lodge in 1979 and given a diagnosis there of severe depression (psychotic depression reaction, according to *DSM-III*). He was treated with individual psychoanalytically oriented psychotherapy four times a week without any biological treatments. He was hospitalized for more than 6 months, during which time he lost over 40 lb., paced incessantly, and showed marked deterioration. The patient was transferred to Silver Hill Foundation, where he received a combination of phenothiazine and tricyclic medication and made a rapid recovery. He subsequently sued Chestnut Lodge for negligence. Inasmuch as the case was settled out of court, no legal precedent has been established.

My testimony was that Chestnut Lodge was negligent because it instituted a treatment, intensive individual psychotherapy, for which there is no evidence of efficacy and withheld biological treatments, which have demonstrated efficacy in severe depressions. My judgment that individual psychotherapy was inappropriate for this patient's condition was based on the existing body of scientific knowledge concerning treatment of hospitalized patients who have severe depression with psychotic features. This evidence has been summarized in numerous volumes and textbooks and in the American Psychiatric Association's manual for peer review. This interpretation of evidence is accepted by Dr. Stone (unpublished manuscript, 1988): "The vast majority of American psychiatrists, including psychoanalysts, accept the evidence that in such psychotic disorders, biological modalities are an essential ingredient of treatment."

I am concerned about the absence of scientific evidence for the efficacy of psychoanalysis and psychoanalytically ori-

ented psychotherapy. It is not that existing evidence is negative, but that evidence is absent. The reasons for the lack of efficacy studies are complex and need not be discussed here. However, newer therapies, especially psychopharmacology and behavioral psychotherapy, have supported their claims with results from controlled clinical trials. Thus, in the competition among treatments, the assessment of efficacy by means of controlled clinical trials has been used by the newer therapies to challenge the dominance of psychoanalysis and psychoanalytically oriented psychotherapy. Unfortunately, the psychoanalytic community has not responded to this challenge with appropriate scientific studies.

I had assumed that Dr. Fink accepted this view. He wrote me (personal communication, October 1988): "I must tell you that I agree with the major thesis you have put forward and I am pleased with the position which you have taken with regard to the need for research in psychoanalysis and psychodynamic psychotherapies. . . . They have stood still and have assumed validation and efficacy." Given this assessment, which Dr. Fink and I share, appropriate studies to assess psychodynamic psychotherapy are overdue.

REFERENCE

1. Fink PJ: Response to the Presidential address: is "biopsychosocial" the psychiatric shibboleth? *Am J Psychiatry* 1988; 145: 1061-1067

GERALD L. KLIERMAN, M.D.
New York, N.Y.

Dr. Fink Replies

SIR: Dr. Klerman's statement is very clear and concise. His quotation from my letter is accurate and I continue to espouse that position. The need for proof of the efficacy of psychodynamic psychotherapy and psychoanalysis remains an unexplored scientific issue that must be dealt with in the next few years. Perhaps the reason it has not been fully explored is our reliance on our subjective experiences and our willingness to accept the unwritten axiom that the patient serves as his or her own control and that psychoanalysis per se is research. Dr. Klerman indicates that psychoanalysis has not responded to the challenge. In the last few months, this has changed. There has been a movement within the American Psychoanalytic Association to work on the development of a study dealing with the outcomes and the efficacy of psychoanalysis. Both the National Institute of Mental Health and the American Psychiatric Association (APA) have ongoing discussions about how to foster the kind of research that will lay this question to rest once and for all.

I believe that it is essential that we support this research and that every member of APA who does psychodynamic psychotherapy and/or psychoanalysis participate actively by reporting on his or her own patients. Since this remains the most pervasive and overriding theoretical base of psychotherapy in the United States, it is important that we listen carefully to Dr. Klerman's views and move toward the recognition that we are in an era which requires greater attention not only to the nature of the therapy prescribed but to the evidence that it is both clinically effective and cost-effective and that we accept this challenge readily.

PAUL J. FINK, M.D.
Philadelphia, Pa.

Citation for Position of Alcoholics Anonymous on Psychotropic Medications

SIR: In their article "Critical Review of Liability for Benzodiazepine Abuse Among Alcoholics" (1), Domenic A. Ciraulo, M.D., and associates stated that "the position of Alcoholics Anonymous (AA) with respect to psychotropic medications is clear" and cited an article in a 1984 edition of the AA *Grapevine*.

If the authors had read the *Grapevine* more closely, they would have noticed a statement found immediately inside the magazine that says, "The AA *Grapevine*[®] presents the experiences and opinions of AA members and others interested in the AA program. Opinions expressed herein are not to be attributed to Alcoholics Anonymous as a whole, nor does publication of any article imply any endorsement by either AA or the AA *Grapevine*[®]."

While this may seem to be a minor issue, Dr. Ciraulo and colleagues are giving a message to others that simply is not true.

REFERENCE

1. Ciraulo DA, Sands BF, Shader RI: Critical review of liability for benzodiazepine abuse among alcoholics. *Am J Psychiatry* 1988; 145:1501-1506

ROBERT O. HORST, B.S.W.
Whiteville, N.C.

Dr. Ciraulo and Associates Reply

SIR: The quotation we cited is from a pamphlet approved by the General Service Conference of Alcoholics Anonymous and was published by Alcoholics Anonymous World Services, Inc. (1). According to its charter, the General Service Conference is "the vehicle by which the AA movement can express its views upon all matters of vital AA policy and all hazardous deviations from AA tradition" (2).

Unfortunately, in our original reference citation the copyright of Alcoholics Anonymous World Services, Inc., was mistakenly listed as the *Grapevine*, which may have led to confusion. Although the *Grapevine* copyright also appears on the title page of the pamphlet to acknowledge a long

passage taken from that publication, Alcoholics Anonymous World Services, Inc., is the appropriate citation.

We wish to assure Mr. Horst and the readers of the *Journal* that the passage we cited accurately reflects AA beliefs. Mr. Horst should be aware that despite the disclaimer which appears in the *Grapevine*, the magazine is viewed as "the mirror of AA thought and action" (3), and many ideas that first appear in the *Grapevine* are later adopted as official AA policy. AA's acceptance of the Twelve Traditions, which had their origin in the *Grapevine*, may be the best example. Approval by the General Service Conference and publication by Alcoholics Anonymous World Services, Inc., make the passage we cited an accurate reflection of the views of the AA fellowship.

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1. The AA Member—Medications and Other Drugs: A Report From a Group of Physicians in AA. New York, Alcoholics Anonymous World Services, 1984
2. Alcoholics Anonymous Comes of Age: A Brief History of AA. New York, Alcoholics Anonymous World Services, 1957, p 296
3. Ibid, p 202

DOMENIC A. CIRAULO, M.D.
BRIAN F. SANDS, M.D.
RICHARD I. SHADER, M.D.
Boston, Mass.

Meaning of "Shibboleth"

SIR: I have a nitpicking comment on Dr. Paul J. Fink's response to the Presidential address (1): the word "shibboleth" was not a meaningless neologism when used as a password by the Gileadites. According to the Oxford English Dictionary (2), it was the Hebrew word for a stream in flood.

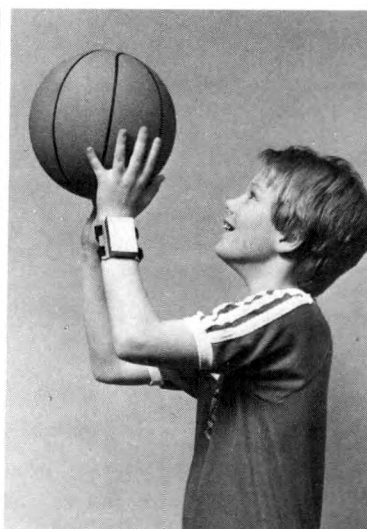
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RICHARD M. WAUGAMAN, M.D.
Rockville, Md.

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¹ Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988;18:14-15.

²FDA Press Release, June 6, 1988.

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- The Anatomy of Madness: Essays in the History of Psychiatry**, vol. III: **The Asylum and Its Psychiatry**, edited by W.F. Bynum, Roy Porter, and Michael Shepherd. New York, Routledge, Chapman & Hall, 1988, 340 pp., \$57.50.
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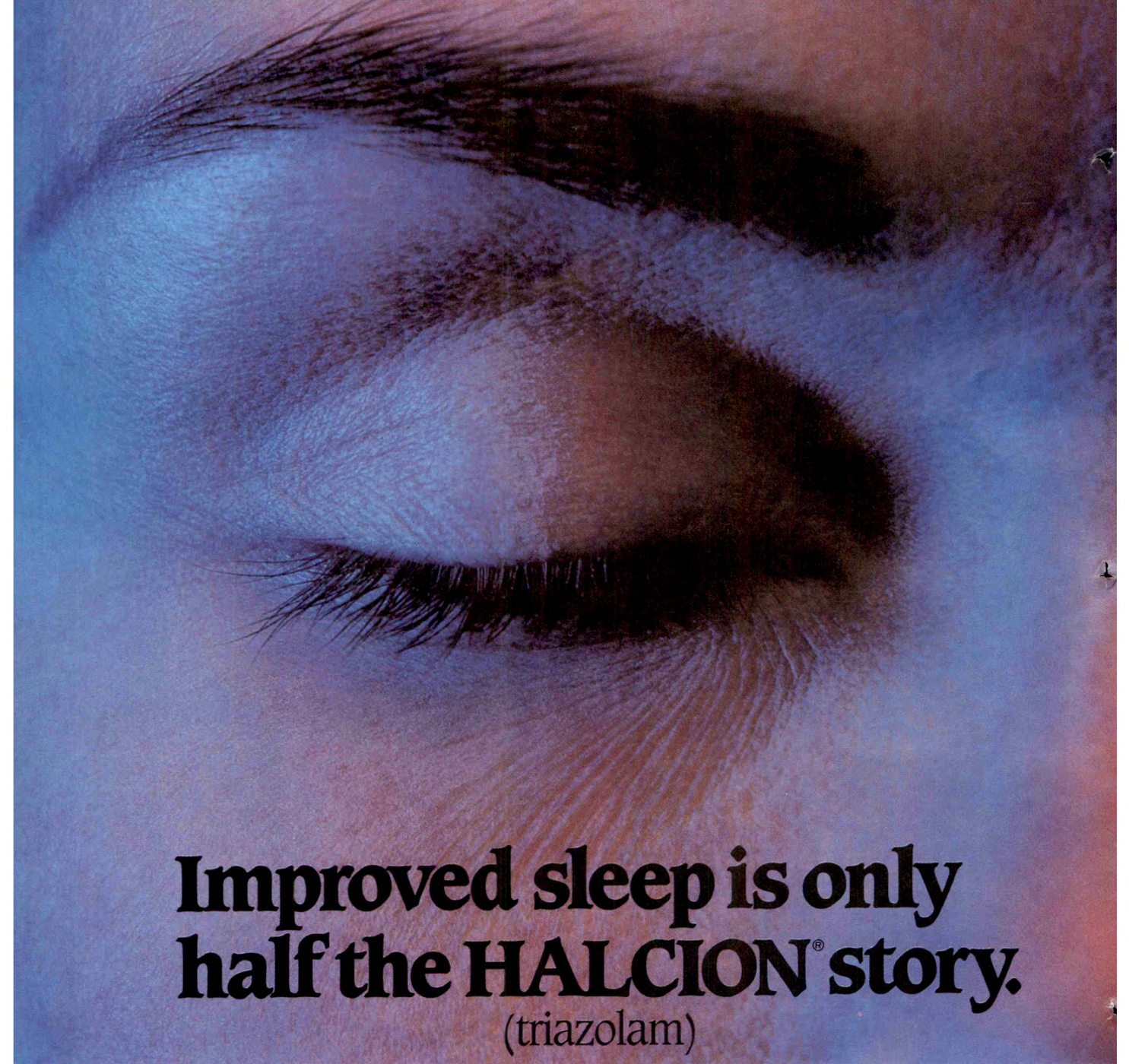
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In depressed patients
HALCION is effective when
adjunctive insomnia
therapy is required.

Disturbed sleep is not an uncommon problem in depressed patients, and although standard tricyclic antidepressants (TCAs) usually relieve insomnia, some depressed patients continue to experience its symptoms. The short-term use of HALCION to relieve insomnia refractory to treatment with TCAs has proven successful in two clinical evaluations.

Effective, concomitant therapy.

HALCION was compared with placebo in a double-blind comparative study of 53 depressed outpatients who had been stabilized on a TCA for at least six weeks but who still suffered refractory insomnia. HALCION was shown to be more effective in relieving the symptoms of insomnia without making depressive symptoms worse.¹

Daytime alertness is the other half.

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Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

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INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizzare or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. **Information for Patients:** Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. **Pregnancy:** Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. **Nursing Mothers:** Administration to nursing mothers is not recommended. **Pediatric Use:** Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dyesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnesic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. **Abuse and Dependence:** Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

B-5-S

References:

- Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
- Dominguez RA, Jacobson AF, Goldstein BJ et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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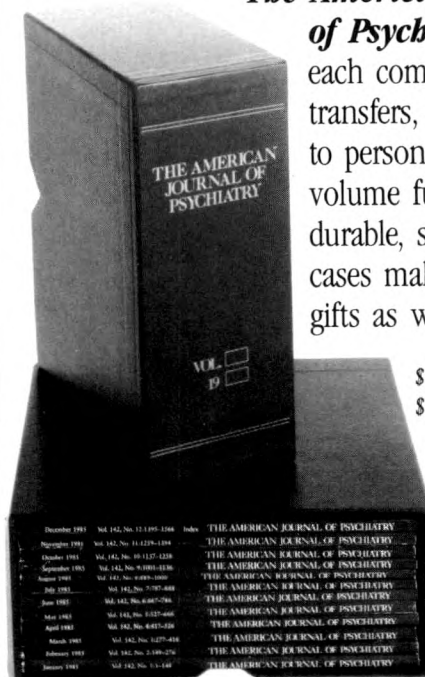
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3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in *Endorphins in Mental Health Research*. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

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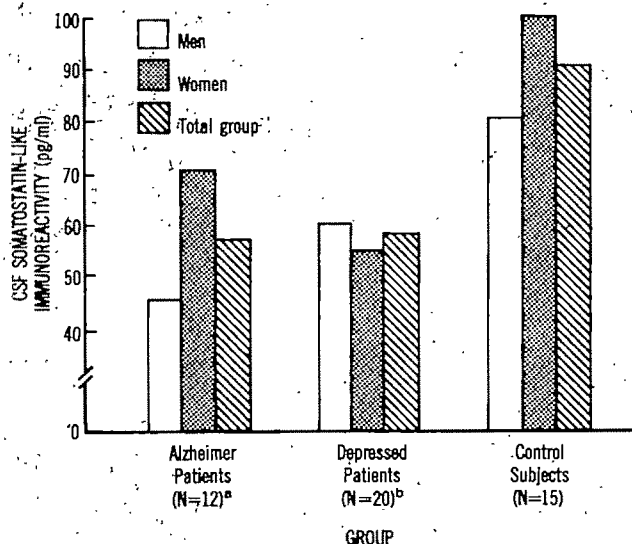
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FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



^aSignificant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

^bSignificant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

duced to 40.5 picas (6¼ inches). When space on the horizontal axis is insufficient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

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2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

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Norpramin®

10, 25, 50, 75, 100, 150 mg
(desipramine hydrochloride tablets USP)

Norpramin® (desipramine hydrochloride tablets USP)

BRIEF SUMMARY
CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS
The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY
Metabolism
The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults. Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke. Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS
Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hypertensive crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually. The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

- WARNINGS**
- Extreme caution should be used when this drug is given in the following situations:
 - In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
 - In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
 - In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
 - In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
 - This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
 - USE IN PREGNANCY**
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
 - USE IN CHILDREN**
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
 - The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
 - In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

- PRECAUTIONS**
- It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
 - If serious adverse effects occur, dosage should be reduced or treatment should be altered.
 - Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
 - The drug may cause exacerbation of psychosis in schizophrenic patients.
 - Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
 - Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
 - Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
 - If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
 - Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
 - This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
 - Both elevation and lowering of blood sugar levels have been reported.
 - Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS
Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, weakness and fatigue, headache, alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE
There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evaluation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here. Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

- Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
- Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.
- Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.
- Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

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A Division of Merrell Dow Pharmaceuticals Inc.
Cincinnati, Ohio 45215

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In Tourette Syndrome

ORAP™

(pimozide) Tablets

Helps Patients Be Themselves*

- **Excellent Symptom Control**

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. ... Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."¹

- **Significantly Less Sedation than Haloperidol**

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long-term patient acceptance...."²

- **Documented Clinical Experience**

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.¹

- **Now Available from LEMMON**

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The Less Sedating Therapy for Tourette Syndrome

* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment. Please see following page for a brief summary of prescribing information.

LEMMON

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ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment of tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 6 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

- ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder.
- ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., phenothiazines, antipsychotics and anesthetic agents) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
- Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
- ORAP is contraindicated in patients with severe toxic central nervous system depression or convulsive states from any cause.
- ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS—Information for Patients).

Tardive Dyskinesia. A syndrome consisting of potentially irreversible, involuntary, dysidetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rule out prevalence estimates to predict, at the initiation of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed to a patient that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical collection, please refer to ADVERSE REACTIONS and PRECAUTIONS—Information for Patients.)

Neuroleptic Malignant Syndrome (NMS). A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, autonomic instability (diaphoretic, tachycardic, labile blood pressure), and evidence of severe muscle rigidity (ranging from lead pipe to blood pressure, tachycardia, clonus, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinuria) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include drug fever, the serotonin toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concurrent serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reprecipitation of drug therapy should be carefully considered. The patient should be carefully monitored, and recurrence of NMS has been reported.

Hypersensitivity, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other. Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a barbiturate potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pentylenetetrazol. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS—Cardiovascular, Impairment of Fertility).

PRECAUTIONS

General. ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concurrently.

Laboratory Tests. An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QTc interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium levels, secondary to diarrhea, or other causes, should be corrected before ORAP therapy is initiated and serum potassium maintained during therapy.

Drug Interactions. Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such

as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, hypnotics, and alcohol.

Cardiovascular, Impairment of Fertility. Cardiovascular studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. These data experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasis, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary hyperplasia. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproductive studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased prenatals and in the related development of fetuses. These effects are thought to be due to an inhibition or delay to implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery. This drug has no recognized use in labor or delivery.

Nursing Mothers. It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for lactogenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General. Extrapyramidal Reactions: Neuroleptic (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported infrequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of extrapyramidal reactions (acute dystonia, dyskinesia, akathisia, hyperreflexia, oculobulbar crises) have been reported for less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of anticholinergic drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that consistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal/Drug-Dependence/Signs. Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dysidetic signs after abrupt withdrawal. In certain of these cases the dysidetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the occurrence of somewhat transient neurological signs, but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dysidetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. This syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antipsychotic agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if any symptoms appear. Should it be necessary to reinstitute treatment, or increase the dose of the agent, or switch to a different antipsychotic agent, this syndrome may be resolved.

It has been reported that the vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizures have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS).

Hypersensitivity: Hypersensitivity has been reported with other antipsychotic drugs.

Other/Other: The following adverse reaction incidence was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Nausea	1	0
Vomiting	0	1
Constipation	4	2
Eruptions	0	1
Tiredness	1	0
Appetite increase	1	0

Body System/Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Ataxia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Ataxia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	6	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions. In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema.
Cardiovascular/Respiratory: Postural hypotension, hypertension, hypernatremia, tachycardia, palpitations.
Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress.
Endocrine: Loss of libido.
Neuroleptic Malignant Syndrome: Weight gain, weight loss.
Central Nervous System: Dizziness, tremor, parkinsonism, fatigue, dyskinesia.
Psychiatric: Excitement.
Skin: Rash, sweating, skin irritation.
Special Senses: Blurred vision, cataracts.
Urogenital: Nocturia, urinary frequency.
Postmarketing Reports. The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.
Hematologic: Hemolytic anemia.

OVERDOSEAGE

In general, the signs and symptoms of overdose with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdose, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinsonian medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on the manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the related side effects is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS—Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic frequency and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

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- Shapiro AK et al: *Psychiatrics* 75:1032-1038, 1967.
- Rose MS et al: *Am J Psychiatry* 135:585-587, 1978.



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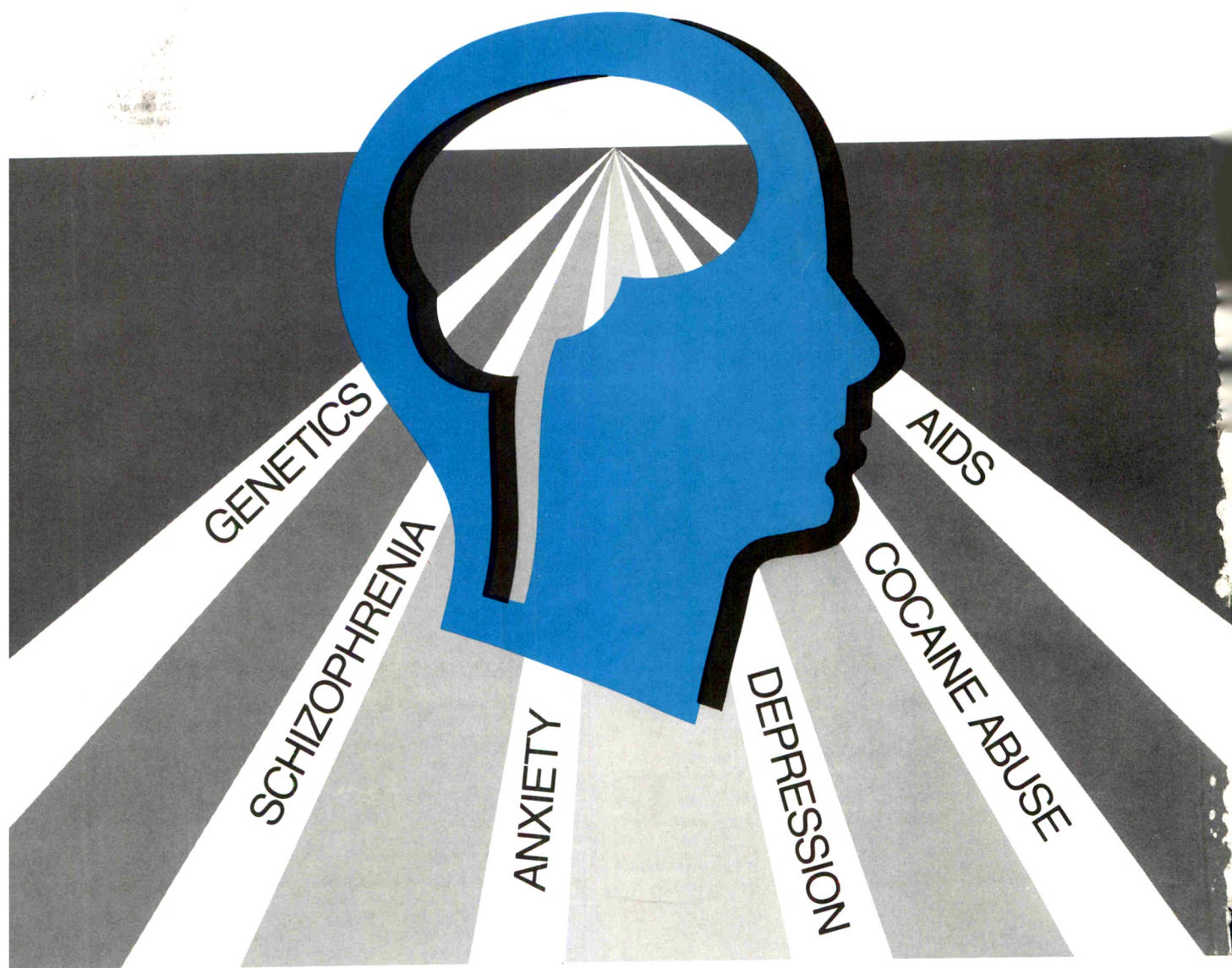
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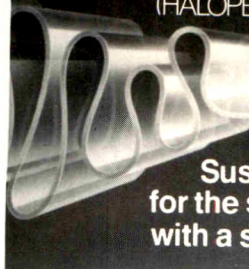
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HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL. The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 2 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancer are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecocystoma, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: *Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions* have been reported frequently, often during the first few days of treatment. Generally they involve Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinsonian drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. Tardive Dystonia—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.*

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecocystoma, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

NOW AVAILABLE!

THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.



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McNEILAB, INC., Spring House, PA 19477